ANNUAL REVIEWS

Annual Review of Public Health

Adverse Cardiovascular Effects of Traffic Noise with a Focus on Nighttime Noise and the New WHO Noise Guidelines

Thomas Münzel,[1,2] Swenja Kröller-Schön,[1] Matthias Oelze,[1] Tommaso Gori,[1,2] Frank P. Schmidt,[1] Sebastian Steven,[1] Omar Hahad,[1] Martin Röösli,[3,4] Jean-Marc Wunderli,[5] Andreas Daiber,[1,2] and Mette Sørensen[6,7]

[1]Center for Cardiology, University Medical Center Mainz, 55131 Mainz, Germany; email: tmuenzel@uni-mainz.de

[2]German Center for Cardiovascular Research (DZHK), Partner Site Rhine-Main, 55131 Mainz, Germany

[3]Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, 4051 Basel, Switzerland

[4]University of Basel, 4001 Basel, Switzerland

[5]Empa, Swiss Federal Laboratories for Materials Science and Technology, 8600 Dübendorf, Switzerland

[6]Diet, Genes and Environment Unit, Danish Cancer Society Research Center, 2100 Copenhagen, Denmark

[7]Department of Natural Science and Environment, Roskilde University, 4000 Roskilde, Denmark

Annu. Rev. Public Health 2020. 41:309–28

First published as a Review in Advance on January 10, 2020

The *Annual Review of Public Health* is online at publhealth.annualreviews.org

https://doi.org/10.1146/annurev-publhealth-081519-062400

Keywords

traffic noise, cardiovascular disease, CVD, sleep disturbance, oxidative stress, circadian clock, mitigation

Abstract

Exposure to traffic noise is associated with stress and sleep disturbances. The World Health Organization (WHO) recently concluded that road traffic noise increases the risk for ischemic heart disease and potentially other cardiometabolic diseases, including stroke, obesity, and diabetes. The WHO report focused on whole-day noise exposure, but new epidemiological and translational field noise studies indicate that nighttime noise, in particular,

is an important risk factor for cardiovascular disease (CVD) through increased levels of stress hormones and vascular oxidative stress, leading to endothelial dysfunction and subsequent development of various CVDs. Novel experimental studies found noise to be associated with oxidative stress–induced vascular and brain damage, mediated by activation of the NADPH oxidase, uncoupling of endothelial and neuronal nitric oxide synthase, and vascular/brain infiltration with inflammatory cells. Noise-induced pathophysiology was more pronounced in response to nighttime as compared with daytime noise. This review focuses on the consequences of nighttime noise.

1. INTRODUCTION

Traffic noise has been classified as the second worst environmental stressor affecting human health, exceeded only by air pollution (37, 98, 102). According to the World Health Organization (WHO), traffic-related noise accounts for more than 1 million healthy years of life lost annually in the European Region; disability-adjusted life-years (DALYs) lost from environmental noise total 61,000 years for ischemic heart disease, 903,000 years for sleep disturbance, and 654,000 years for annoyance (102). New research has found that traffic noise may also increase risk for other major diseases, including stroke (88) and diabetes (107), which would add substantially to the DALY estimate.

In the newly published WHO guidelines (32), the guideline development group concluded that traffic noise increases the risk of ischemic heart disease, and potentially hypertension, stroke, overweight, and diabetes (52). The WHO also evaluated the exposure–response relationships between environmental noise and disease (103), based on which they strongly recommended to decrease L_{DEN} (noise over the whole day; **Supplemental Table 1**) below 53 dB for road traffic, below 54 dB for railway noise, and below 45 dB for aircraft noise to prevent adverse health effects. These thresholds are lower than existing recommended thresholds; e.g., the European Union recommends a threshold of 55 dB for environmental noise.

Supplemental Material >

In 2009, the WHO published a report focusing on night noise, which states that "there is evidence from animal and human studies supporting a hypothesis that night exposure might be more strongly associated with cardiovascular effects than daytime exposure, highlighting the need for future epidemiological studies on this topic" (101, p. 101). A number of mechanistic field studies (44, 80, 81), experimental studies (54, 60), and epidemiological studies (42, 43, 69) have subsequently investigated the cardiovascular effects of nighttime traffic noise. The 2018 WHO report focused on the effects of L_{DEN} (24 h noise) in their evaluation of cardiometabolic disease, so in this review we summarize the current knowledge of the pathway from exposure to nighttime noise to cardiovascular and metabolic disease, identify research gaps, and present mitigation measures.

According to the noise effect reaction scheme introduced by Babisch (reviewed in 61), noise can act through a direct and an indirect pathway. For very high noise levels [>85 dB(A)], the direct pathway can lead to hearing loss. Lower levels of noise will initiate the indirect pathway that represents the cognitive perception of the sound and the physiological reaction resulting in cortical activation and disturbances of sleep, activities, and communication, leading to cognitive and emotional stress response, such as noise annoyance (**Figure 1*a***) (61). The activation of the indirect pathway by noise is characterized by an increase in sympathetic responses and release of corticoids (61), yielding an increase in blood viscosity, activation of blood coagulation, and increased blood pressure (58). Stress responses do not require the involvement of cortical structures, i.e., the cognitive perception of noise is not a prerequisite for its adverse cardiovascular effects. Thus, noise

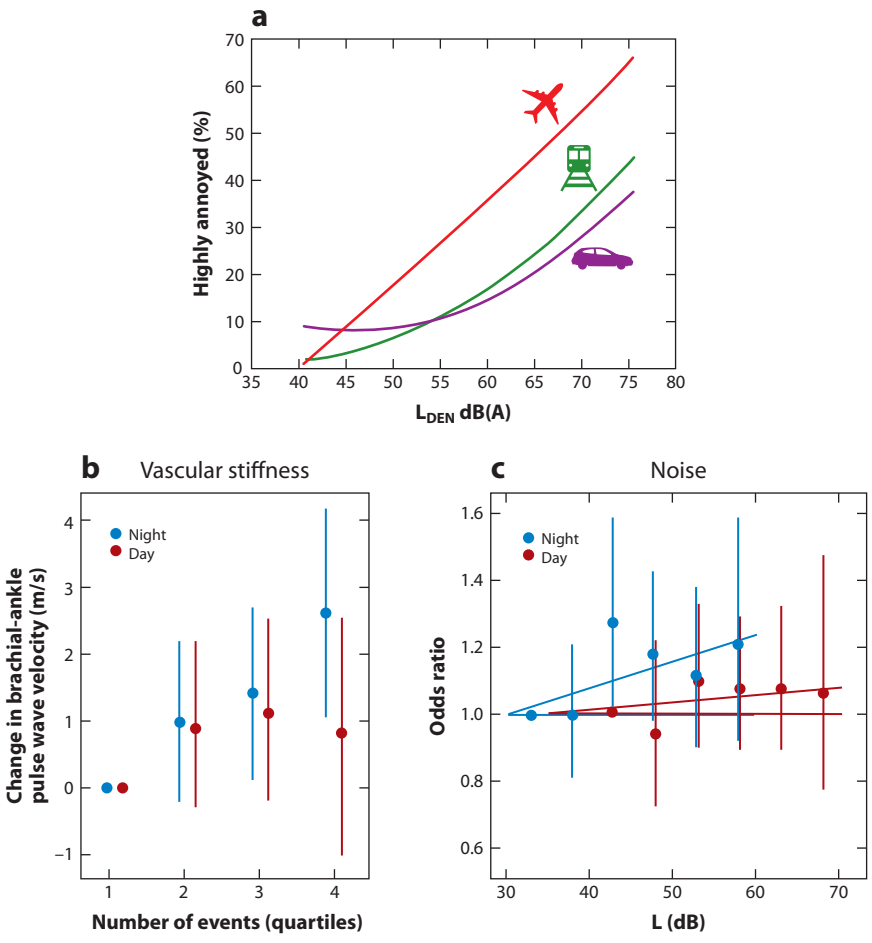


Figure 1

Clinical impact of traffic noise exposure. (*a*) Percent highly annoyed by L_{DEN} noise levels from rail, road, and aircraft. Graphs were constructed on the basis of the equations given as part of the 2018 WHO environmental noise guidelines (35). Panel *a* adapted from Reference 35 with permission according to the Creative Commons Attribution License. (*b*) Association between brachial-ankle pulse wave velocity (baPWV) and the number of daytime and nighttime noise events by quartiles (27). Panel *b* adapted from *Environmental Health Perspectives* (27) with permission from the authors. (*c*) Odds ratios (ORs) of hypertension in relation to aircraft noise (5-dB categories). LAeq,16h and L_{night} were included separately in the model. Adjusted for country, age, sex, body mass index, alcohol intake, education, and exercise. The error bars denote 95% confidence intervals (CIs) for the categorical (5-dB) analysis. The blue and red lines show the ORs and corresponding 95% CIs for the continuous analyses. Panel *c* adapted from *Environmental Health Perspectives* (49) with permission from the authors.

may exert its effects directly through synaptic interactions or indirectly through the emotional and cognitive perception of sound. Thus, both the objective noise exposure (sound level) and its perception determine the impact of noise in neuroendocrine hemostasis and therefore the degree of stress reaction. If noise stress persists for years, cardiovascular diseases (CVD) may develop, including stable coronary artery disease, acute coronary syndromes, arrhythmia, heart failure, arterial hypertension, and stroke (62).

2. NIGHTTIME TRAFFIC NOISE AND CVD: EPIDEMIOLOGICAL STUDIES

2.1. New WHO Guidelines

The epidemiological evidence of an association between exposure to transportation noise and risk of cardiovascular and metabolic diseases was evaluated in a systematic review commissioned by the WHO and published in 2018 (52, 103). The quality of evidence was assessed using Grading of Recommendations, Assessment, Development and Evaluations (GRADE). For incident ischemic heart disease (IHD), road traffic noise was found significantly associated with an 8% increase in risk for every 10 dB(A) increase in noise, starting from 53 dB(A). The WHO expert group ranked the quality of this evidence as high. Rail and aircraft noise were also consistently found to increase the risk of IHD, but the quality of evidence was ranked lower than for road traffic noise owing to fewer studies of high quality. Similarly, the review found associations between road traffic noise and increased risk for incident stroke and diabetes, but the evidence was ranked as moderate owing to the lack of high-quality studies. However, high-quality cohort studies published after the WHO report offer further support for an association between traffic noise and increased risk of stroke, especially ischemic stroke, and diabetes (10, 17, 25, 36, 41, 51, 65, 72, 85).

The WHO expert group included 37 studies on transportation noise and hypertension in their meta-analyses, giving a relative risk for road traffic noise and prevalent hypertension of 1.05 (1.02–1.08) per 10 dB(A) increase in noise (based on 26 cross-sectional studies). However, the quality of the evidence was rated as "very low" because almost all studies were cross-sectional, preventing interpretations regarding causality (52). Since publication of the WHO report, a few studies on transportation noise and risk for incident hypertension have been published (20, 30, 66, 108), but results are inconsistent.

Studies published after the WHO report suggest that exposure to transportation noise may result in a higher risk of CVDs not investigated by the WHO: heart failure and atrial fibrillation. These studies found road traffic and/or aircraft noise to increase the risk for heart failure incidence and mortality (41, 84, 90) and potentially increase the risk for incident atrial fibrillation (20, 59).

Supplemental Material >

The focus of the WHO report was to evaluate the effects of exposure to transportation noise over the whole day, estimated as L_{DEN} (**Supplemental Table 1**). The WHO evaluated the effects of nighttime noise previously in 2009. However, since 2009, a number of mechanistic studies have investigated the effects of nocturnal noise, indicating that it may be a particularly crucial time window, as exposure to noise during nighttime disturbs and stresses the body during sleep, thereby increasing a number of cardiovascular risk factors (44, 54, 80, 81). In the following sections, we summarize the current knowledge of the cardiovascular effects of nighttime noise.

2.2. Nighttime Noise and Sleep

Sleep is vital to ensure human health, and deficiencies in sleep are associated with cardiovascular and metabolic diseases (11, 79, 92). The WHO recently evaluated the effects of transportation noise on measured and self-reported sleep (3). A meta-analysis of psychoacoustic surveys on self-reported sleep disturbance (percent highly disturbed) showed statistically significant odds ratios of 1.9 for aircraft, 2.1 for road, and 3.1 for rail per 10 dB(A) increase in noise when questions referred to the effects of noise on sleep (3). However, in studies where the sleep questions did not refer to specific noise sources but to general sleep indicators, such as problems with falling asleep and awakenings, associations with traffic noise were less pronounced.

Furthermore, as part of the WHO review, a combined analysis was conducted of two existing studies examining acute effects of traffic noise events on sleep physiology measured by polysomnography (5, 22). This event-related analysis showed that a 10 dB(A) increase in indoor

maximum noise from road, rail, or aircraft was significantly associated with awakenings or sleep stage changes (from deeper sleep stages to wake or stage 1) with odds ratios of 1.35 (3). Based on this analysis, the WHO strongly recommended to decrease nighttime noise (L_{night}) for road traffic noise below 45 dB(A), for railway noise below 44 dB(A), and for aircraft noise below 40 dB(A) to prevent effects on sleep (103).

Sleep spindles: sudden bursts of oscillatory brain activity that occur during stage 2 of light sleep measured by EEG

A 2018 study (73), published after the WHO review, with young (19–33 years) and older (52–70 years) volunteers confirmed effects from nighttime transportation noise events on increased sleep electroencephalography (EEG) arousal indices, although sleep structure and continuity were not affected [Leq was 45 dB; maximum event levels were 50–62 dB(A)] (73). Amplitude of sleep spindles, which are known to have a sleep-protective function (100) and to be relevant for memory consolidation (2), was consistently decreased during noise compared with noise-free nights in both age groups.

Which time window during sleep is most critical is still unclear, although such knowledge is important for efficient noise control. A study of 12 women and 12 men who slept for 2 weeks in a sleep laboratory applied 3 different noise scenarios with noise curfews at different times during the night (11 PM–3 AM, 11 PM–5 AM, 3 AM–7 AM) and analyzed the polysomnograms (33). Investigators found that noise in the beginning of the night impaired the process of falling asleep. However, sleep disturbances experienced in the beginning of the night were compensated later if nighttime curfews were in place. In contrast, even short periods of noise toward the end of the sleeping period were observed to cause sleep disturbances. In line with this finding, several observational studies on transportation noise indicate that noise exposure has the strongest effect on self-reported sleep quality in the morning, when the sleep pressure is lowest. In a Norwegian study of 13,019 participants (24) and a Swiss study of 1,375 participants (29), modeled nighttime traffic noise exposure was associated primarily with self-reported early awakenings, whereas associations with other sleep-quality parameters such as awakening during the night or difficulty falling asleep were less pronounced. Also, psychoacoustic surveys observed that noise exposure occurring during the early part of the night and during the time just preceding usual awakening were reported to be most annoying (63). Strikingly, a panel study of 40 individuals found that noise exposure during work had sustained effects on nighttime sleep quality, suggesting that daytime noise may also be relevant for sleep (57).

2.3. Nighttime Noise and Risk for CVD

Although exposure to transportation noise is known to disturb sleep duration and quality, epidemiological studies comparing the effects of daytime and nighttime transportation noise are necessary to improve our understanding of which exposure time window is most harmful.

Separating long-term effects of daytime and nighttime noise exposure in epidemiological studies are challenging. Exposure misclassification for daytime noise is higher than for nighttime noise because large-scale epidemiological studies are based on residential exposure, which may not reflect personal exposure during the day, when people are likely not to be at home. Also, daytime and nighttime exposure levels are often highly correlated. This finding is especially evident for road traffic noise where input data on traffic are based on traffic count samples, which are then extrapolated over the whole day, resulting in correlations between daytime and nighttime noise close to 1 (36, 42, 89). In reality, correlation between road traffic noise at different time intervals is expected to be lower (71).

A Spanish cross-sectional study overcame this correlation dilemma by calculating three different estimates for residential traffic noise for their population of ≈2,000 persons: noise at the most exposed façade; noise at the bedroom façade; and "indoor bedroom noise" where information on

insulation, type of window, and window-opening habits was included (28). They found a significant association with a higher systolic blood pressure only for indoor bedroom noise, suggesting that nighttime noise affects the blood pressure. However, they also found noise at the most exposed façade to be more strongly associated with hypertension than was indoor bedroom noise, suggesting that exposure during the day and evening can also be harmful.

For aircraft and railway noise, correlations between daytime and nighttime noise are lower than for road traffic noise. The Hypertension and Exposure to Noise Near Airports (HYENA) study of ≈5,000 persons living near one of six major European airports investigated effects of nighttime aircraft noise (20, 39, 40, 49). In this study, correlation between daytime and nighttime aircraft noise was 0.8 and a significant association between nighttime aircraft noise and prevalent hypertension was found, whereas no association was seen for daytime aircraft noise (**Figure 1*c***) (49). A follow-up study of the Greek population of the HYENA study later supported this finding in a longitudinal design: The data showed a significant association between nighttime aircraft noise and incident hypertension, whereas associations with daytime aircraft noise were weaker and insignificant (20). Within the framework of the HYENA study, 140 participants were selected for a field study with continuous measurements of noise and blood pressure during sleep at home (40). The study found a 6-mm Hg increase in systolic and a 7-mm Hg increase in diastolic blood pressure if an aircraft event of >35 dB(A) had occurred within the last 15 minutes. Results of similar size were observed for road traffic noise. This association was independent of the sequence of noise measurements, indicating that there is no habituation happening during the night. Using the same study population, both measured nighttime bedroom exposure and modeled long-term exposure to road traffic noise were found to be associated with a decrease in systolic and diastolic dipping, whereas no association was found for aircraft noise (39). Subsequent longitudinal studies on aircraft noise and risk of CVD found similar associations for modeled daytime noise compared with nighttime noise, which indicates that, for aircraft noise, separating the effects of daytime and nighttime noise is problematic when using standard noise modeling (38, 108). This limitation highlights the importance of improved or new noise assessment methods that better capture the difference in noise over the course of the day.

A recent Swiss study developed a method for estimating an "intermittency ratio" (IR) during nighttime, which quantifies the contribution of individual noise events above the background noise level (105). The IR varies from 0%, corresponding to continuous noise (no events above background), to 100%, corresponding to all noise made by single noise events. It thereby captures a potentially very important aspect of noise, as single distinct noise events during sleep have been linked to awakenings and cardiac arousals (4, 5), and nighttime noise events have been found to affect arterial stiffness (**Figure 1*b***) (27). Data from 4.4 million people indicated that moderate IR levels during nighttime were found to be more strongly associated with overall cardiovascular mortality than were low IR and high IR (41). The project also investigated associations with CVD for noise exposure at different time windows during the day, estimated as combined long-term noise exposure from road, rail, and air based on modeled hourly traffic data (42). Despite the inherent difficulties in separating the effects of different noise time windows (correlations ≥0.94), the combination of the three noise sources yielded more variation, thereby facilitating the analyses. For IHD, the highest mortality risks were found for noise exposure during the core nighttime period, whereas for heart failure, exposure during the daytime period was associated with the highest risk (42). Overall, this finding suggests that for acute CVD, nocturnal intermittent noise exposure is more relevant than daytime exposure, whereas for more chronic CVD, continuous daytime exposure is most relevant. In support, measured brachial-ankle pulse wave velocity in 2,775 participants (49–81 years old) was significantly associated with the number of noise events during the nighttime (at residence) but not with the number of noise events during the day (**Figure 1*b***) (27).

In summary, the few epidemiological studies that have successfully managed to separate daytime and nighttime exposure to noise have found that nighttime noise is indeed an important risk factor for some CVDs and that intermittent noise with peaks clearly above the background level during the nighttime may be particularly harmful.

3. TRANSLATIONAL STUDIES: EFFECTS OF SIMULATED NIGHTTIME NOISE ON VASCULAR FUNCTION

Few experimental studies have addressed the impact of nighttime traffic noise on vascular function. In two field studies, the effects of nocturnal aircraft noise on vascular function were studied in healthy subjects and patients with established coronary artery disease. The study participants were exposed to playback of 30 and 60 aircraft noise events. The subjects wore portable polygraphic screening devices during the night with continuous recording of electrocardiogram (ECG), SpO2, actimetry, light, and derived parameters (80, 81). In these studies, nighttime aircraft noise caused a marked decrease in sleep quality (80, 81), a worsening of endothelial function, an increase in adrenalin levels, and a decrease in pulse transit time, reflecting sympathetic activation. The adverse effects of nighttime noise on endothelial function were more pronounced in subjects with coronary artery disease. In a smaller subgroup of healthy subjects nested within these studies, supplementing with the antioxidant vitamin C significantly improved endothelial dysfunction [see the sidebar titled Endothelial Dysfunction and Inflammation (Macrosialin)], suggesting that nighttime noise induces endothelial dysfunction mainly by stimulating vascular production of reactive oxygen species (ROS), leading to a decrease in vascular NO bioavailability. The worsening of endothelial function was independent of sleep quality and self-reported noise sensitivity or noise annoyance (80). Sleep deprivation has been shown to cause endothelial dysfunction in healthy subjects, and the degree of deterioration of endothelial function is comparable to that observed in workers working 24-h shifts (1) and in humans exposed to chronic sleep restriction (95). Recent data indicate that simulated train noise for one night not only impairs endothelial dysfunction and sleep quality in healthy subjects but also induces prothromboinflammatory changes of the plasma proteome, indicating that this short exposure period is enough to cause adverse changes in protein expression (44).

In a six-day laboratory study of 21 healthy volunteers, participants were assigned to either an unexposed group or an exposed group, starting with a noise-free baseline night, then four nights with transportation noise, and ending with a noise-free recovery night (96). Glucose tolerance and insulin sensitivity were measured. After a noise exposure night, total glucose secretion was increased and insulin sensitivity was decreased compared with baseline.

Reactive oxygen species (ROS): a group of biomolecules formed in the organism with the potential to cause oxidative damage. ROS comprise among others superoxide anion radicals, hydrogen peroxide, hydroxyl radicals, singlet oxygen, and alkyl peroxides

ENDOTHELIAL DYSFUNCTION AND INFLAMMATION (MACROSIALIN)

The important homeostatic properties of the inner cell layer of the vessels, the endothelium, are lost due to (oxidative or mechanic) damage, which is characterized by impaired vasodilation of the vasculature in response to exogenous or endogenous vasodilators and is usually accompanied by a proinflammatory, prothrombotic, and proatherosclerotic phenotype.

CD68 (Cluster of Differentiation 68) is a protein that is highly expressed by cells in the monocyte lineage (e.g., monocytic phagocytes, osteoclasts), by circulating macrophages, and by tissue macrophages (e.g., Kupffer cells, microglia). CD68 is involved in cell adhesion and recruitment and activation of macrophages for phagocytosis or removal of cell debris.

OXIDATIVE STRESS (PLASMA 3-NITROTYROSINE) AND ANTIOXIDANT DEFENSE (FOXO SIGNALING PATHWAYS)

Nitro-oxidative stress by reactive nitrogen species such as peroxynitrite or nitrogen dioxide radicals leads to nitration of aromatic amino acids such as tyrosine leaving 3-nitrotyrosine (3-NT)-positive proteins as a footprint of these reactive and short-lived species. 3-nitrotyrosine-positive proteins in the plasma or tissue can be measured by ELISA (enzyme-linked immunosorbent assay) or immunohistochemistry using specific antibodies against nitrated tyrosine residues representing a readout of nitro-oxidative stress in vivo. Levels of 3-nitrotyrosine-positive proteins correlate with most cardiovascular disease.

Members of the class O of forkhead box transcription factors (FOXO) have important roles in metabolism, cellular proliferation, stress resistance, and apoptosis. They are conserved regulators of longevity downstream of insulin signaling. Forkhead box O3 (FOXO3) is specifically involved in protection from oxidative stress by upregulation of antioxidant enzymes such as catalase and manganese superoxide dismutase.

4. MECHANISTIC INSIGHT FROM ANIMAL STUDIES

4.1. Effects of Around-the-Clock Noise on Stress Hormones, Oxidative Stress, and Cerebrovascular Complications

A study on mice exposed to noise for 1–4 days found that around-the-clock aircraft noise resulted in higher levels of circulating neurohormonal stress hormones, endothelial dysfunction, vascular inflammation, and oxidative stress [60; see the sidebar titled Oxidative Stress (Plasma 3-Nitrotyrosine) and Antioxidant Defense (FOXO Signaling Pathways)]. The phagocytic NADPH oxidase (Nox2 subunit) and an uncoupled endothelial nitric oxide synthase (eNOS) were identified as major sources of ROS formation. The central role of oxidative stress and phagocytic NADPH oxidase (NOX-2; see the sidebar titled Phagocytic NADPH Oxidase) for noise-induced cerebrovascular complications in animals was demonstrated by a subsequent study (54). As expected, noise exposure shares many pathophysiological features with the health effects of severe life stress, which may explain noise-triggered cognitive impairment in children (93) and mental disease in adults (6, 83, 94).

Severe life stress (including sleep deprivation) triggers vascular and cerebral oxidative stress (77, 87), followed by vascular and neuronal inflammation and activation of the angiotensin-II pathway, leading to an activation of the NADPH oxidase (mainly Nox2) (13, 87). Chronic noise exposure has also been shown to increase the circulating levels of angiotensin-II and cortisol in animals (60, 74) and humans (86) and even represents a markedly strong trigger of NOX-2

PHAGOCYTIC NADPH OXIDASE

NADPH oxidases are a family of multisubunit heme enzymes with the sole biological function of producing superoxide anion radicals ($O_2^{\bullet -}$) by oxidation of NADPH and transfer of its electrons to molecular oxygen. Some isoforms also directly form hydrogen peroxide. Whereas recent data point toward cellular signaling functions of hydrogen peroxide at low levels (e.g., in cell differentiation, proliferation, and migration), excessive formation of these ROS is detrimental for the cell and biomolecules such as DNA, leading to oxidative modifications of these biomolecules, loss of cellular function, and oxidative stress. The phagocytic NADPH oxidase (NOX-2 isoform) is highly expressed in phagocytic cells such as macrophages and granulocytes, and upon bacterial or fungal stimuli, it produces large amounts of ROS, in a process called oxidative burst, to facilitate the killing of pathogens.

NITRIC OXIDE SYNTHASE

This group of heme enzymes produces nitric oxide, an important vasodilator and an antiaggregatory and antiatherosclerotic messenger, by oxidation of the amino acid L-arginine by molecular oxygen and the cofactors tetrahydrobiopterin (BH4) and flavins. Nitric oxide activates the soluble guanylyl cyclase, with subsequent generation of the second messenger cGMP exerting most of the beneficial effects of nitric oxide. Of note, nitric oxide itself is also a free radical (•NO). Nitric oxide synthases (NOS) exist as 3 isoforms: neuronal, inducible, and endothelial NOS, also termed NOS-1, NOS-2, and NOS-3, which can switch from nitric oxide to superoxide formation by a process known as uncoupling. Uncoupled NOS is thought to be a major driver of various cardiovascular diseases.

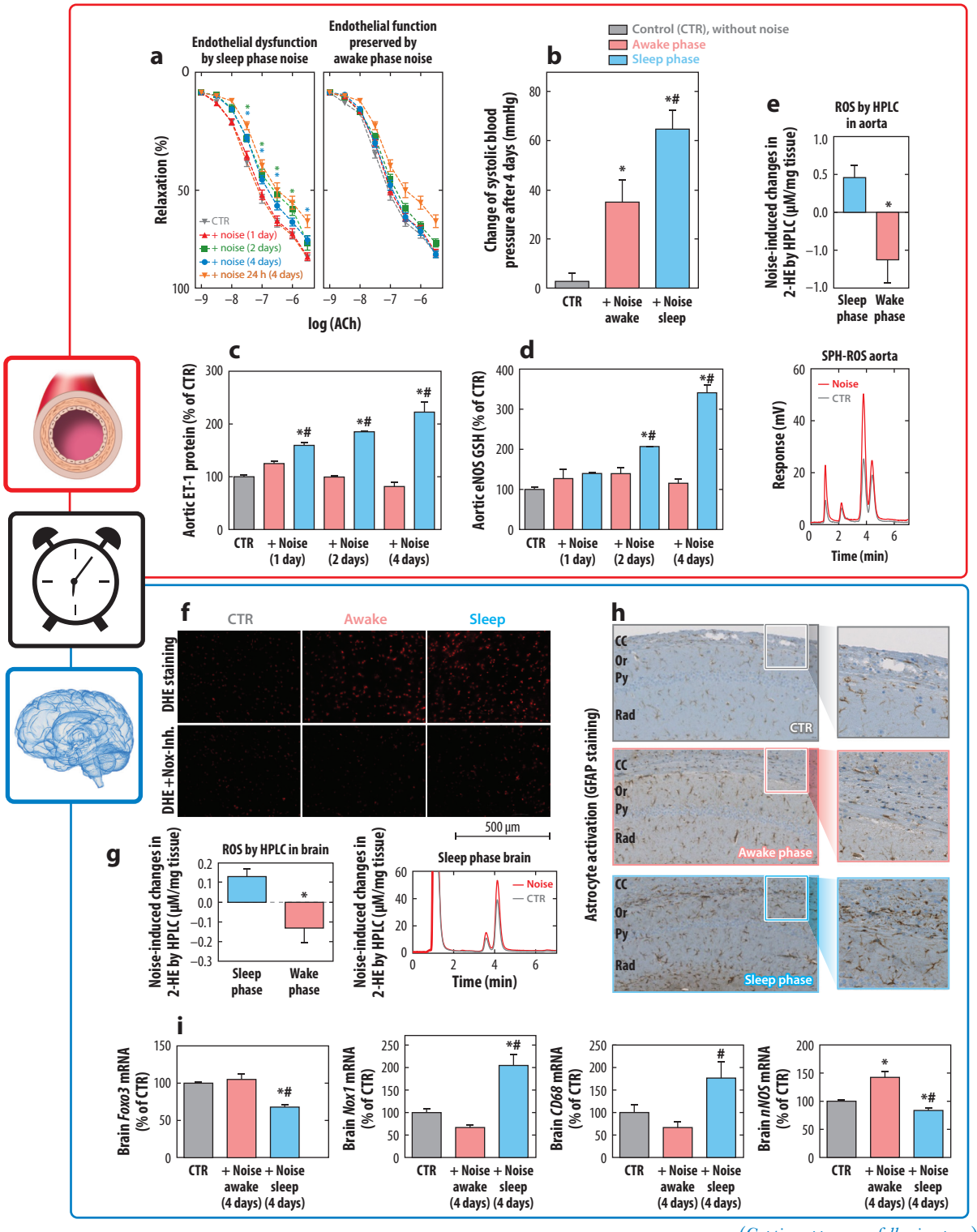
activity (34, 68, 106). Accordingly, in the mouse model of around-the-clock aircraft noise exposure, genetic *Nox2* deletion normalized endothelial dysfunction, plasma 3-nitrotyrosine and interleukin 6 (IL-6) levels, and vascular ROS production (**Supplemental Figure 1*a–d***) (54). In addition, noise-induced cerebral oxidative stress and neuronal nitric oxide synthase (nNOS; see the sidebar titled Nitric Oxide Synthase) uncoupling, decreased nNOS expression, and increased markers of inflammation such as IL-6, *inducible nitric oxide synthase* (*iNOS*), and *macrosialin* (*CD68*) were normalized by genetic *Nox2* deletion (**Supplemental Figure 1*e–h*** and **Supplemental Text**) (54).

Supplemental Material >

When white noise was used for exposure in mice (same duration, same mean sound pressure level), the above-mentioned adverse effects were not observed at all, suggesting that parameters other than noise energy (e.g., frequency or pattern) are responsible for noise-induced cardiovascular damage. Using next-generation sequencing, changes in the expression of hundreds of genes being involved in important cellular processes were found, including apoptosis, cell growth, fibrosis, inflammation, and antioxidant defense, including transcription factors and key phosphatases (e.g., involved in NF-κB and FOXO signaling pathways) (60).

4.2. Effects of Sleep versus Awake Phase Noise on the Cardiovascular System and the Brain

In an experimental study, animals were exposed to noise during the sleep and awake phases respectively, representing nighttime and daytime noise (54). Noise during the sleep phase but not during the awake phase caused endothelial dysfunction and increased blood pressure, vascular endothelin-1 expression, and oxidative stress and increased eNOS uncoupling by S-glutathionylation (**Figure 2*a–e***), a crucial mechanism underlying eNOS uncoupling (15, 109). Circulating markers of oxidative stress, such as 3-nitrotyrosine, and of inflammation, such as IL-6, were also increased only by sleep phase noise exposure (54). In addition, only noise during the sleep phase increased cerebral oxidative stress and led to substantial astrocyte activation in the corpus callosum, downregulation of cerebral *Foxo3* and *nNOS*, and upregulation of *Nox1* and *CD68* mRNA in the brain (**Figure 2*f–i***) (54). Similar changes have been observed in animal models upon sleep deprivation (12) and have also been linked with increased cardiovascular events and mortality (16, 26). Therefore, sleep deprivation and fragmentation represent the most likely explanation for the adverse cardiovascular/cerebrovascular effects observed in mouse models of nocturnal and around-the-clock aircraft noise exposure. Pharmacological inhibition of NOX-2 was found to prevent cerebral oxidative stress by sleep phase noise exposure (**Figure 2*f***), validating the findings in *Nox2*-deficient mice (**Supplemental Figure 1**).



(Caption appears on following page)

Figure 2 (*Figure appears on preceding page*)

Effects of sleep and awake phase aircraft noise [mean sound pressure level 72 dB(A) for 12 h per day for 1, 2, and 4 days] on the murine vasculature and the brain. In the vessel (*top*, *red outline*): Sleep phase noise caused significantly more pronounced endothelial dysfunction as determined by impaired endothelium-dependent relaxation (response to the vasodilator acetylcholine, or ACh) by isometric tension measurement (*a*). Endothelial dysfunction is indicated by a shift to the right of the concentration-relaxation curves evident for sleep phase but not awake phase noise exposure. For comparison, the impaired endothelium-dependent relaxation in response to 24 h noise exposure is also shown. Sleep phase noise showed a more pronounced increase in blood pressure by tail cuff measurement (*b*), endothelin-1 (ET-1) protein expression by immunohistochemistry (*c*), and aortic eNOS uncoupling by immunostaining against S-glutathionylated (= uncoupled) enzyme (eNOS-GSH) (*d*). Sleep phase noise also increased aortic superoxide formation more strongly as compared with awake phase noise as quantified by high-performance liquid chromatography (HPLC)-dependent measurement of 2-hydroxyethidium (2-HE), a superoxide-specific product of hydroethidum (DHE) as shown by the peak at 3.8 min in the representative chromatograms (*e*). In the brain (*bottom*, *blue outline*): Sleep phase noise also induced more pronounced reactive oxygen species (ROS) formation in the brain (frontal cortex; DHE staining for cytoplasmic ROS by oxidative fluorescent microtopography) than did awake phase noise, all of which was eliminated by inhibition of the ROS source NOX-2 (*f*). Noise-induced cerebral superoxide production as measured by HPLC-dependent quantification of 2-HE was higher in response to noise during sleep than during the awake phase (*g*). Astrocytes were activated in sleep phase noise-exposed mice in the corpus callosum (*h*). Representative images for immunohistochemical staining for glial fibrillary acidic protein (GFAP) are shown at the level of the hippocampus sector CA1. Hippocampus sector abbreviations: CC, corpus callosum; Or, stratum oriens; Py, pyramidale; Rad, radiatum. Marker of inflammation (*CD68*) and ROS-producing *Nox1* were increased, whereas the antioxidant/protective genes *Foxo3* and *nNOS* were decreased at the mRNA level by sleep phase noise as revealed by reverse transcription polymerase chain reaction (RT-PCR) (*i*). Figure adapted from Reference 54 with permission.

4.3. Noise and the Circadian Clock System

As summarized by Qin & Deng (67), the circadian rhythm process relies on a group of clock genes, such as the transcriptional activators circadian locomotor output cycles kaput (*Clock*), brain and muscle aryl hydrocarbon receptor nuclear translocator (*Arnt*)-like (*Bmal*) 1, period (*Per*), and cryptochrome (*Cry*) (18), and controls the time-dependent expression profile of multiple genes and, accordingly, messengers/hormones (in a 24-h rhythm) with the help of SIRT-1 and the melatonin system (104). Sleep deprivation causes changes very similar to those triggered by circadian rhythm dysregulation, namely severe inflammatory conditions (67), endothelial dysfunction, blood pressure increases, structural vascular changes, vascular senescence, and recruitment of immune cells in mice (12), and with prominent manifestation in patients with obstructive sleep apnea, being that sleep fragmentation is a hallmark of this disease (99). In the experimental study, around-the-clock noise also increased blood glucose levels, potentially owing to alterations in insulin signaling (54), all of which can affect circadian clock genes (14). The association between disrupted circadian rhythm and altered insulin signaling in animals is further supported by human data on the adverse effects of sleep restriction on insulin sensitivity and the risk of diabetes (9, 11, 91). The circadian rhythm is maintained by a transcription–translation feedback: the CLOCK/BMAL complex induces PER and CRY, suppressing the activity of the CLOCK/BMAL complex (**Supplemental Figure 2*d***) (76). Thereby, the circadian clock system regulates and controls a number of fundamental processes related to inflammation via the NF-κB pathway (64; see also the sidebar titled Circadian Clock Regulation), DNA repair proteins and antioxidant defense (104), stress hormone levels, and other endocrine factors (19); it also affects the aging process, heart disease, cancer, neurodegenerative diseases, and diabetes (104). Accordingly, the circadian clock has a large impact on our health (**Supplemental Figure 2*e***).

Supplemental Material >

Disruption of the circadian clock provides a plausible explanation for the adverse effects of around-the-clock and sleep phase noise. In an experimental animal study, the effects of noise on disruption of the circadian clock were investigated by employing a next-generation sequencing technique (54). A conserved dysregulation of genes of the circadian clock after noise exposure in the aorta and kidney was identified, although the overall number of significantly regulated genes

CIRCADIAN CLOCK REGULATION

In most living organisms, internally synchronized circadian clocks allow the anticipation of daily changes in the environment (day/night cycle) and adjustment of biological processes and behavior accordingly. The circadian clock system is regulated by numerous redox processes (direct oxidation of cysteine residues or activation of redox-sensitive kinases), phosphorylation by different kinases, and other posttranslational modifications. Redox-sensitive kinases such as AMP-activated protein kinase (AMPK) or mitogen-activated protein kinase (MAPK) regulate circadian clock activity by phosphorylation of circadian proteins at different amino acids. Another regulator is ADP-ribosylating enzyme poly(ADP-ribose) polymerase 1 (PARP-1), which is essential for initiating various forms of DNA repair. The antioxidant enzyme heme oxygenase-1 (HO-1) catalyzes the breakdown of iron-porphyrins (heme) to carbon monoxide and biliverdin, which also controls circadian clock activity. Other regulators are the histone deacetylase sirtuin-1 (SIRT-1), the transcription factor hypoxia-inducible factor-1α (HIF-1α), and the transcription coactivator peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α), which are all subject to redox regulation.

Supplemental Material >

was quite different between these tissues (**Supplemental Figure 2*a*,*b***) (54). Taking into consideration that around-the-clock and sleep phase noise exposures were associated with substantial oxidative stress in the brain, heart, and vasculature, adverse redox regulation of the central and peripheral clocks provides an attractive explanation for the observed dysregulation of circadian genes by noise. Mammalian CRY1 has several redox-sensitive cysteine thiol groups as well as a zinc/sulfur complex that control binding of PER and FBXL3 and thereby their inhibitory potency on the CLOCK/BMAL1 complex (78). In addition, redox-sensitive kinases AMPK (55) or MAPK (75) as well as stress–response proteins such as PARP-1 (50), HO-1, HIF-1α (70), PGC-1α, and histone deacetylase SIRT-1 (56) might be involved (see the sidebar titled Circadian Clock Regulation for a definition of terms used in this section). The study also found a potential link between *Foxo3* expression and FOXO3 activity and important genes of the circadian clock system that were all up- or downregulated by around-the-clock aircraft noise in a time-dependent fashion (**Supplemental Figure 2*c***). A role for FOXO3 in the circadian clock is in accordance with previous reports demonstrating that circadian clock oscillation is irregular and that the period is variable upon deletion of *Foxo3* (14). The central role of FOXO3 in noise-induced endothelial dysfunction and vascular/cerebral oxidative stress in general, and dysregulated circadian clock in particular, was supported by the finding that the FOXO3 activator bepridil normalized these adverse effects in noise-exposed mice (**Supplemental Figure 2*f*,*g***) (54).

5. NOISE MITIGATION MEASURES

Calculations indicate that >30% of the European population is exposed to residential L_{DEN} levels exceeding 55 dB(A), with road traffic being the most dominant source of environmental noise (21). Because these noise levels lead to a considerable increase in incidence and mortality of CVD (21), development of mitigation strategies is necessary.

The general trend of increasing road traffic volumes is unbroken (31). With the exception of the lowest speed regimes, rolling noise, i.e., the sound generated by the interaction of tires and pavement, is the dominating noise source (45). The introduction of electric cars, which affects only engine noise, will therefore not lead to an important reduction in noise levels. Consequently, the most promising strategies for noise reduction at the source are the installation of quiet road surfaces, promotion of low-noise tires, and speed reductions in densely populated areas. Another strategy applied in some countries is the introduction of driving bans for trucks during the core nighttime hours.

Air travel has expanded tenfold in the past 40 years (46). The International Civil Aviation Organization proposes, as a noise mitigation strategy, a balanced approach with four consecutive mitigation steps (48). Reduction of noise at the source is the first priority. Indeed, noise emissions of commercial aircraft have substantially decreased over the last few decades, due primarily to initiatives to reduce fuel consumption (46). Second, land-use planning and management could help to separate air traffic routes and housing zones (7). Third, noise abatement operational flight procedures could be developed and implemented, which optimize the vertical flight profiles and points in time of aircraft configuration changes (47, 53). Last, operating restrictions are usually envisaged. Although most airports try to avoid limiting the total number of flights, many airports have already implemented night curfews (8).

Compared with road and air transportation, increases in rail traffic volumes have been less pronounced (23). Railway traffic is characterized by dominating passenger transport during the day and freight transport during the night. While passenger wagons are typically equipped with low-noise disc brakes, the majority of freight wagons in Europe still use cast-iron block breaks, which introduce high wheel roughness and high sound radiation. Replacing these cast-iron blocks with composite materials can reduce the sound emissions by 8–10 dB(A).

If mitigation measures at the source are not successful, measures along the propagation path are important. The most common approach is noise barriers, with an effect of up to 20 dB(A) directly behind the barrier. Barriers are useless, however, for residents in upper floors, require land space, and, among other limitations, have negative impacts on accessibility and landscape scenery. Finally, adaptation measures can be taken at the resident's home. Apart from general measures to improve sound insulation, typically by installing soundproof windows, the focus should be on orienting noise-sensitive rooms such as sleeping or living rooms toward the quiet side of the building (97). The European Commission recently published an overview of the quantitative potential of the above-described mitigation strategies (**Supplemental Figure 3**) (82).

Supplemental Material >

6. CONCLUSIONS

Disturbance of sleep is a key determinant of the hazardous effects of traffic noise on risk for CVD, and nighttime traffic noise has been associated with reduced sleep quality, awakenings, and sleep stage changes. Exposure to noise toward the end of the sleeping period may be most crucial with regard to effects of noise on sleep.

The evidence provided from epidemiological, translational, and basic science models shows that nighttime noise compared with daytime noise is associated with more adverse cardiovascular effects. Compared with daytime noise, nighttime noise leads to a stronger stress reaction as indicated by higher neurohormone levels, higher increases in oxidative stress, more pronounced vascular stiffness, and arterial hypertension, as well as perhaps a higher incidence of cardiovascular and metabolic diseases (**Figure 3**). Also, some evidence suggests that intermittent noise with peaks clearly above the background levels during the nighttime may be particularly harmful.

Results from animal models have shed light on some of the mechanisms behind the effects of nighttime noise on CVD, including a disturbance of the circadian clock due to downregulation of genes responsible for regulating the circadian rhythm. Furthermore, analyses of aortic and brain tissues from animals exposed to noise revealed significant changes in the expression of genes responsible for the regulation of vascular function, vascular remodeling, and cell death.

High relevance of nighttime noise for health does not imply that daytime noise is not relevant. Daytime noise also activates the sympathetic nervous system. This physiological response may also persist into the sleep periods and negatively affect the restorative potential of sleep. Because the proportion of the population being exposed to high levels of transportation noise is

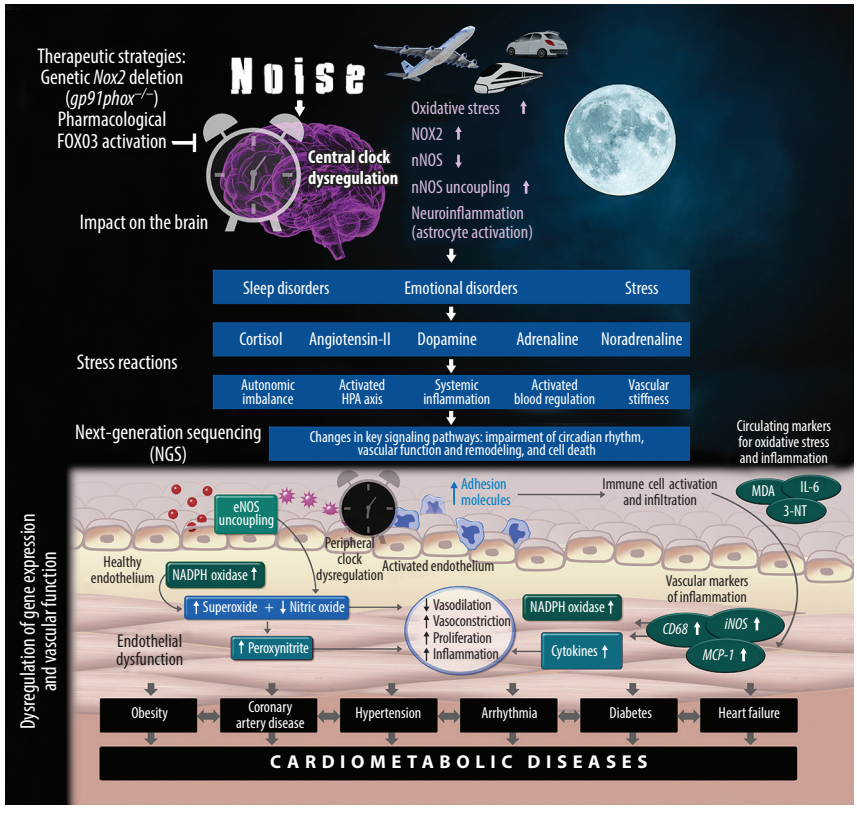


Figure 3

Pathophysiology of nighttime noise–induced cardiovascular and brain disease. Genetic *Nox2* deficiency and pharmacological FOXO3 activation by bepridil prevented the adverse noise effects. Abbreviations: 3-NT, 3-nitrotyrosine; CD68, macrosialin; eNOS, endothelial nitric oxide synthase; HPA, hypothalamic-pituitary-adrenal; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde. Figure updated from Reference 54 with permission.

substantial, existing and new innovative strategies to reduce noise should be implemented, with a focus on reducing both daytime and nighttime exposures. Future research should focus on clarifying the mechanisms behind the effects of nighttime noise on CVD, especially identifying critical time windows during sleep and exploring the effects of different characteristics of noise, such as intermittent noise events compared with more continuous noise. Also, epidemiological intervention studies, such as investigating the effects of implementing nighttime noise curfews or adding sound insulation on windows, are needed.

In summary, epidemiological, translational, and basic science studies find that nighttime noise is a very important exposure window in relation to adverse cardiovascular effects, although various research gaps still need attention.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

AUTHOR CONTRIBUTIONS

T.M., M.S., and A.D. conceived the presented idea. M.S. drafted the introduction. M.S. and M.R. drafted the section on nighttime traffic noise and CVD. T.M. and A.D. drafted the sections on translational studies and mechanistic studies. J.W. drafted the section on mitigation methods. All authors provided critical feedback and helped to shape the final manuscript.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the expert graphical assistance of Margot Neuser. We also acknowledge the financial support of our ongoing noise studies by the Foundation Heart of Mainz and the Boehringer Ingelheim Foundation for the collaborative research group "Novel and neglected cardiovascular risk factors: molecular mechanisms and therapeutic implications" (T.M., S.S., and A.D.). T.M. is PI of the DZHK (German Center for Cardiovascular Research), Partner Site Rhine-Main, Mainz, Germany.

LITERATURE CITED

1. Amir O, Alroy S, Schliamser JE, Asmir I, Shiran A, et al. 2004. Brachial artery endothelial function in residents and fellows working night shifts. *Am. J. Cardiol.* 93:947–49
2. Antony JW, Schönauer M, Staresina BP, Cairney SA. 2019. Sleep spindles and memory reprocessing. *Trends Neurosci.* 42:1–3
3. Basner M, McGuire S. 2018. WHO environmental noise guidelines for the European region: a systematic review on environmental noise and effects on sleep. *Int. J. Environ. Res. Public Health* 15:519
4. Basner M, Müller U, Elmenhorst E-M. 2011. Single and combined effects of air, road, and rail traffic noise on sleep and recuperation. *Sleep* 34:11–23
5. Basner M, Samel A, Isermann U. 2006. Aircraft noise effects on sleep: application of the results of a large polysomnographic field study. *J. Acoust. Soc. Am.* 119:2772–84
6. Beutel ME, Junger C, Klein EM, Wild P, Lackner K, et al. 2016. Noise annoyance is associated with depression and anxiety in the general population—the contribution of aircraft noise. *PLOS ONE* 11:e0155357
7. Bissegger M. 2013. Noise management in the light of airport development. In *INTER-NOISE: the 42nd International Congress and Exposition on Noise Control Engineering, Innsbruck, Austria, September 15–18, 2013, Proceedings*. Vienna: Austrian Noise Abat. Assoc.
8. Brink M, Schäffer B, Pieren R, Wunderli JM. 2018. Conversion between noise exposure indicators Leq_{24h}, L_{Day}, $L_{Evening}$, L_{Night}, L_{dn}, and L_{DEN}: principles and practical guidance. *Int. J. Hyg. Environ. Health* 221:54–63
9. Buxton OM, Pavlova M, Reid EW, Wang W, Simonson DC, Adler GK. 2010. Sleep restriction for 1 week reduces insulin sensitivity in healthy men. *Diabetes* 59:2126–33
10. Cai Y, Hodgson S, Blangiardo M, Gulliver J, Morley D, et al. 2018. Road traffic noise, air pollution and incident cardiovascular disease: a joint analysis of the HUNT, EPIC-Oxford and UK Biobank cohorts. *Environ. Int.* 114:191–201
11. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. 2010. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care* 33:414–20
12. Carreras A, Zhang SX, Peris E, Qiao Z, Gileles-Hillel A, et al. 2014. Chronic sleep fragmentation induces endothelial dysfunction and structural vascular changes in mice. *Sleep* 37:1817–24
13. Chan SH, Chan JY. 2013. Angiotensin-generated reactive oxygen species in brain and pathogenesis of cardiovascular diseases. *Antioxid. Redox Signal.* 19:1074–84
14. Chaves I, van der Horst GT, Schellevis R, Nijman RM, Koerkamp MG, et al. 2014. Insulin-FOXO3 signaling modulates circadian rhythms via regulation of clock transcription. *Curr. Biol.* 24:1248–55
15. Chen CA, Wang TY, Varadharaj S, Reyes LA, Hemann C, et al. 2010. S-glutathionylation uncouples eNOS and regulates its cellular and vascular function. *Nature* 468:1115–18

16. Chien KL, Chen PC, Hsu HC, Su TC, Sung FC, et al. 2010. Habitual sleep duration and insomnia and the risk of cardiovascular events and all-cause death: report from a community-based cohort. *Sleep* 33:177–84
17. Clark C, Sbihi H, Tamburic L, Brauer M, Frank LD, Davies HW. 2017. Association of long-term exposure to transportation noise and traffic-related air pollution with the incidence of diabetes: a prospective cohort study. *Environ. Health Perspect.* 125:087025
18. Cuninkova L, Brown SA. 2008. Peripheral circadian oscillators: interesting mechanisms and powerful tools. *Ann. N. Y. Acad. Sci.* 1129:358–70
19. Daiber A, Kroller-Schon S, Frenis K, Oelze M, Kalinovic S, et al. 2019. Environmental noise induces the release of stress hormones and inflammatory signaling molecules leading to oxidative stress and vascular dysfunction—signatures of the internal exposome. *Biofactors* 45:495–506
20. Dimakopoulou K, Koutentakis K, Papageorgiou I, Kasdagli MI, Haralabidis AS, et al. 2017. Is aircraft noise exposure associated with cardiovascular disease and hypertension? Results from a cohort study in Athens, Greece. *Occup. Environ. Med.* 74:830–37
21. EEA (Eur. Environ. Agency). 2014. *Noise in Europe 2014*. Rep. 10, EEA, Luxembourg. **https://www.eea.europa.eu/publications/noise-in-europe-2014**
22. Elmenhorst EM, Pennig S, Rolny V, Quehl J, Mueller U, et al. 2012. Examining nocturnal railway noise and aircraft noise in the field: sleep, psychomotor performance, and annoyance. *Sci. Total Environ.* 424:48–56
23. EUROSTAT. 2018. *Energy, transport and environment indicators, 2018 edition*. Rep., Eur. Comm., Luxembourg. **https://ec.europa.eu/eurostat/documents/3217494/9433240/KS-DK-18-001-EN-N.pdf/73283db2-a66b-4d34-9818-b61a08883681**
24. Evandt J, Oftedal B, Hjertager Krog N, Nafstad P, Schwarze PE, Marit Aasvang G. 2017. A population-based study on nighttime road traffic noise and insomnia. *Sleep* 40:zsw055
25. Eze IC, Foraster M, Schaffner E, Vienneau D, Heritier H, et al. 2017. Long-term exposure to transportation noise and air pollution in relation to incident diabetes in the SAPALDIA study. *Int. J. Epidemiol.* 46:1115–25
26. Ferrie JE, Shipley MJ, Cappuccio FP, Brunner E, Miller MA, et al. 2007. A prospective study of change in sleep duration: associations with mortality in the Whitehall II cohort. *Sleep* 30:1659–66
27. Foraster M, Eze IC, Schaffner E, Vienneau D, Héritier H, et al. 2017. Exposure to road, railway, and aircraft noise and arterial stiffness in the SAPALDIA Study: annual average noise levels and temporal noise characteristics. *Environ. Health Perspect.* 125:097004
28. Foraster M, Künzli N, Aguilera I, Rivera M, Agis D, et al. 2014. High blood pressure and long-term exposure to indoor noise and air pollution from road traffic. *Environ. Health Perspect.* 122:1193–200
29. Frei P, Mohler E, Röösli M. 2014. Effect of nocturnal road traffic noise exposure and annoyance on objective and subjective sleep quality. *Int. J. Hyg. Environ. Health* 217:188–95
30. Fuks KB, Weinmayr G, Basagaña X, Gruzieva O, Hampel R, et al. 2017. Long-term exposure to ambient air pollution and traffic noise and incident hypertension in seven cohorts of the European study of cohorts for air pollution effects (ESCAPE). *Eur. Heart J.* 38:983–90
31. Grandner MA. 2017. Sleep, health, and society. *Sleep Med. Clin.* 12:1–22
32. Greiber S, Münzel T, Kästner S, Müller B, Schollmeyer P, Pavenstädt H. 1998. NAD(P)H oxidase activity in cultured human podocytes: effects of adenosine triphosphate. *Kidney Int.* 53:654–63
33. Griefahn B, Marks A, Robens S. 2008. Temporally limited nocturnal traffic curfews to prevent noise induced sleep disturbances. In *Sleep: 9th International Congress on Noise as a Public Health Problem (ICBEN) 2008, Foxwoods, CT*. **http://www.icben.org/2008/PDFs/Griefahn_Robens.pdf**
34. Griendling KK, Minieri CA, Ollerenshaw JD, Alexander RW. 1994. Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. *Circ. Res.* 74:1141–48
35. Guski R, Schreckenberg D, Schuemer R. 2017. WHO environmental noise guidelines for the European Region: a systematic review on environmental noise and annoyance. *Int. J. Environ. Res. Public Health* 14:E1539
36. Halonen JI, Hansell AL, Gulliver J, Morley D, Blangiardo M, et al. 2015. Road traffic noise is associated with increased cardiovascular morbidity and mortality and all-cause mortality in London. *Eur. Heart J.* 36:2653–61

37. Hänninen O, Knol AB, Jantunen M, Lim TA, Conrad A, et al. 2014. Environmental burden of disease in Europe: assessing nine risk factors in six countries. *Environ. Health Perspect.* 122:439–46
38. Hansell AL, Blangiardo M, Fortunato L, Floud S, de Hoogh K, et al. 2013. Aircraft noise and cardiovascular disease near Heathrow airport in London: small area study. *BMJ* 347:f5432
39. Haralabidis AS, Dimakopoulou K, Velonaki V, Barbaglia G, Mussin M, et al. 2011. Can exposure to noise affect the 24 h blood pressure profile? Results from the HYENA study. *J. Epidemiol. Community Health* 65:535–41
40. Haralabidis AS, Dimakopoulou K, Vigna-Taglianti F, Giampaolo M, Borgini A, et al. 2008. Acute effects of night-time noise exposure on blood pressure in populations living near airports. *Eur. Heart J.* 29:658–64
41. Héritier H, Vienneau D, Foraster M, Eze IC, Schaffner E, et al. 2017. Transportation noise exposure and cardiovascular mortality: a nationwide cohort study from Switzerland. *Eur. J. Epidemiol.* 32:307–15
42. Héritier H, Vienneau D, Foraster M, Eze IC, Schaffner E, et al. 2018. Diurnal variability of transportation noise exposure and cardiovascular mortality: a nationwide cohort study from Switzerland. *Int. J. Hyg. Environ. Health* 221:556–63
43. Héritier H, Vienneau D, Foraster M, Eze IC, Schaffner E, et al. 2019. A systematic analysis of mutual effects of transportation noise and air pollution exposure on myocardial infarction mortality: a nationwide cohort study in Switzerland. *Eur. Heart J.* 40:598–603
44. Herzog J, Schmidt FP, Hahad O, Mahmoudpour SH, Mangold AK, et al. 2019. Acute exposure to nocturnal train noise induces endothelial dysfunction and pro-thromboinflammatory changes of the plasma proteome in healthy subjects. *Basic Res. Cardiol.* 114:46
45. Heutschi K, Locher B, Gerber M. 2018. sonROAD18: Swiss implementation of the CNOSSOS-EU Road Traffic Noise Emission model. *Acta Acustica United With Acustica* 104:697–706
46. IATA (Int. Air Transp. Assoc.). 2011. *Vision 2050*. Rep., IATA, Singapore. **https://www.iata.org/contentassets/bccae1c5a24e43759607a5fd8f44770b/vision-2050.pdf**
47. ICAO (Int. Civil Aviat. Organ.). 2007. *Review of noise abatement procedure research & development and implementation results*. Rep., ICAO, Montréal. **https://www.icao.int/environmental-protection/Documents/ReviewNADRD.pdf**
48. ICAO (Int. Civil Aviat. Organ.). 2009. *Guidance on the balanced approach to aircraft noise management*. Doc. 9829 AN/451, 2nd ed., ICAO, Montréal
49. Jarup L, Babisch W, Houthuijs D, Pershagen G, Katsouyanni K, et al. 2008. Hypertension and exposure to noise near airports: the HYENA study. *Environ. Health Perspect.* 116:329–33
50. Jordan SD, Lamia KA. 2013. AMPK at the crossroads of circadian clocks and metabolism. *Mol. Cell Endocrinol.* 366:163–69
51. Jørgensen JT, Bräuner EV, Backalarz C, Laursen JE, Pedersen TH, et al. 2019. Long-term exposure to road traffic noise and incidence of diabetes in the Danish Nurse Cohort. *Environ. Health Perspect.* 127:57006
52. Kempen EV, Casas M, Pershagen G, Foraster M. 2018. WHO environmental noise guidelines for the European Region: a systematic review on environmental noise and cardiovascular and metabolic effects: a summary. *Int. J. Environ. Res. Public Health* 15:379
53. Khardi S, Abdallah L. 2012. Optimization approaches of aircraft flight path reducing noise: comparison of modeling methods. *Appl. Acoustics* 73:291–301
54. Kröller-Schön S, Daiber A, Steven S, Oelze M, Frenis K, et al. 2018. Crucial role for Nox2 and sleep deprivation in aircraft noise-induced vascular and cerebral oxidative stress, inflammation, and gene regulation. *Eur. Heart J.* 39:3528–39
55. Lamia KA, Sachdeva UM, DiTacchio L, Williams EC, Alvarez JG, et al. 2009. AMPK regulates the circadian clock by cryptochrome phosphorylation and degradation. *Science* 326:437–40
56. Lee Y, Kim EK. 2013. AMP-activated protein kinase as a key molecular link between metabolism and clockwork. *Exp. Mol. Med.* 45:e33
57. Lin CY, Tsai PJ, Lin KY, Chen CY, Chung LH, et al. 2018. Will daytime occupational noise exposures induce nighttime sleep disturbance? *Sleep Med.* 50:87–96
58. Lundberg U. 1999. Coping with stress: neuroendocrine reactions and implications for health. *Noise Health* 1:67–74

59. Monrad M, Sajadieh A, Christensen JS, Ketzel M, Raaschou-Nielsen O, et al. 2016. Residential exposure to traffic noise and risk of incident atrial fibrillation: a cohort study. *Environ. Int.* 92–93:457–63
60. Münzel T, Daiber A, Steven S, Tran LP, Ullmann E, et al. 2017. Effects of noise on vascular function, oxidative stress, and inflammation: mechanistic insight from studies in mice. *Eur. Heart J.* 38:2838–49
61. Münzel T, Gori T, Babisch W, Basner M. 2014. Cardiovascular effects of environmental noise exposure. *Eur. Heart J.* 35:829–36
62. Münzel T, Schmidt FP, Steven S, Herzog J, Daiber A, Sørensen M. 2018. Environmental noise and the cardiovascular system. *J. Am. Coll. Cardiol.* 71:688–97
63. Muzet A. 2007. Environmental noise, sleep and health. *Sleep Med. Rev.* 11:135–42
64. Narasimamurthy R, Hatori M, Nayak SK, Liu F, Panda S, Verma IM. 2012. Circadian clock protein cryptochrome regulates the expression of proinflammatory cytokines. *PNAS* 109:12662–67
65. Pyko A, Andersson N, Eriksson C, de Faire U, Lind T, et al. 2019. Long-term transportation noise exposure and incidence of ischaemic heart disease and stroke: a cohort study. *Occup. Environ. Med.* 76:201–7
66. Pyko A, Lind T, Mitkovskaya N, Ögren M, Östenson CG, et al. 2018. Transportation noise and incidence of hypertension. *Int. J. Hyg. Environ. Health* 221:1133–41
67. Qin B, Deng Y. 2015. Overexpression of circadian clock protein cryptochrome (CRY) 1 alleviates sleep deprivation-induced vascular inflammation in a mouse model. *Immunol. Lett.* 163:76–83
68. Rajagopalan S, Kurz S, Münzel T, Tarpey M, Freeman BA, et al. 1996. Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. Contribution to alterations of vasomotor tone. *J. Clin. Invest.* 97:1916–23
69. Recio A, Linares C, Banegas JR, Diaz J. 2016. The short-term association of road traffic noise with cardiovascular, respiratory, and diabetes-related mortality. *Environ. Res.* 150:383–90
70. Reinke H, Asher G. 2019. Crosstalk between metabolism and circadian clocks. *Nat. Rev. Mol. Cell Biol.* 20:227–41
71. Röösli M, Brink M, Rudzik F, Cajochen C, Ragettli MS, et al. 2019. Associations of various nighttime noise exposure indicators with objective sleep efficiency and self-reported sleep quality: a field study. *Int. J. Environ. Res. Public Health* 16:3790
72. Roswall N, Raaschou-Nielsen O, Jensen SS, Tjønneland A, Sørensen M. 2018. Long-term exposure to residential railway and road traffic noise and risk for diabetes in a Danish cohort. *Environ. Res.* 160:292–97
73. Rudzik F, Thiesse L, Pieren R, Wunderli JM, Brink M, et al. 2018. Sleep spindle characteristics and arousability from nighttime transportation noise exposure in healthy young and older individuals. *Sleep* 41:zsy077
74. Said MA, El-Gohary OA. 2016. Effect of noise stress on cardiovascular system in adult male albino rat: implication of stress hormones, endothelial dysfunction and oxidative stress. *Gen. Physiol. Biophys.* 35:371–77
75. Sanada K, Harada Y, Sakai M, Todo T, Fukada Y. 2004. Serine phosphorylation of mCRY1 and mCRY2 by mitogen-activated protein kinase. *Genes Cells* 9:697–708
76. Sato TK, Yamada RG, Ukai H, Baggs JE, Miraglia LJ, et al. 2006. Feedback repression is required for mammalian circadian clock function. *Nat. Genet.* 38:312–19
77. Schiavone S, Jaquet V, Trabace L, Krause KH. 2013. Severe life stress and oxidative stress in the brain: from animal models to human pathology. *Antioxid. Redox Signal.* 18:1475–90
78. Schmalen I, Reischl S, Wallach T, Klemz R, Grudziecki A, et al. 2014. Interaction of circadian clock proteins CRY1 and PER2 is modulated by zinc binding and disulfide bond formation. *Cell* 157:1203–15
79. Schmid SM, Hallschmid M, Schultes B. 2015. The metabolic burden of sleep loss. *Lancet Diabetes Endocrinol.* 3:52–62
80. Schmidt F, Kolle K, Kreuder K, Schnorbus B, Wild P, et al. 2015. Nighttime aircraft noise impairs endothelial function and increases blood pressure in patients with or at high risk for coronary artery disease. *Clin. Res. Cardiol.* 104:23–30
81. Schmidt FP, Basner M, Kröger G, Weck S, Schnorbus B, et al. 2013. Effect of nighttime aircraft noise exposure on endothelial function and stress hormone release in healthy adults. *Eur. Heart J.* 34:3508–14

82. Sci. Commun. Unit, Univ. West Engl., Bristol. 2017. *Noise abatement approaches*. Sci. For Environ. Policy Future Brief, Issue 17, Eur. Comm. Dir.-Gen. Environ., Brussels. **https://ec.europa.eu/environment/integration/research/newsalert/pdf/noise_abatement_approaches_FB17_en.pdf**
83. Seidler A, Hegewald J, Seidler AL, Schubert M, Wagner M, et al. 2017. Association between aircraft, road and railway traffic noise and depression in a large case-control study based on secondary data. *Environ. Res.* 152:263–71
84. Seidler A, Wagner M, Schubert M, Dröge P, Römer K, et al. 2016. Aircraft, road and railway traffic noise as risk factors for heart failure and hypertensive heart disease—a case-control study based on secondary data. *Int. J. Hyg. Environ. Health* 219:749–58
85. Seidler AL, Hegewald J, Schubert M, Weihofen VM, Wagner M, et al. 2018. The effect of aircraft, road, and railway traffic noise on stroke—results of a case-control study based on secondary data. *Noise Health* 20:152–61
86. Selander J, Bluhm G, Theorell T, Pershagen G, Babisch W, et al. 2009. Saliva cortisol and exposure to aircraft noise in six European countries. *Environ. Health Perspect.* 117:1713–17
87. Singel KL, Segal BH. 2016. NOX2-dependent regulation of inflammation. *Clin. Sci.* 130:479–90
88. Sørensen M, Hvidberg M, Andersen ZJ, Nordsborg RB, Lillelund KG, et al. 2011. Road traffic noise and stroke: a prospective cohort study. *Eur. Heart J.* 32:737–44
89. Sørensen M, Ketzel M, Overvad K, Tjønneland A, Raaschou-Nielsen O. 2014. Exposure to road traffic and railway noise and postmenopausal breast cancer: a cohort study. *Int. J. Cancer* 134:2691–98
90. Sørensen M, Wendelboe Nielsen O, Sajadieh A, Ketzel M, Tjønneland A, et al. 2017. Long-term exposure to road traffic noise and nitrogen dioxide and risk of heart failure: a cohort study. *Environ. Health Perspect.* 125:097021
91. Spiegel K, Tasali E, Leproult R, Van Cauter E. 2009. Effects of poor and short sleep on glucose metabolism and obesity risk. *Nat. Rev. Endocrinol.* 5:253–61
92. St-Onge MP, Grandner MA, Brown D, Conroy MB, Jean-Louis G, et al. 2016. Sleep duration and quality: impact on lifestyle behaviors and cardiometabolic health: a scientific statement from the American Heart Association. *Circulation* 134:e367–86
93. Stansfeld SA, Berglund B, Clark C, Lopez-Barrio I, Fischer P, et al. 2005. Aircraft and road traffic noise and children's cognition and health: a cross-national study. *Lancet* 365:1942–49
94. Stansfeld SA, Haines MM, Burr M, Berry B, Lercher P. 2000. A review of environmental noise and mental health. *Noise Health* 2:1–8
95. Takase B, Akima T, Uehata A, Ohsuzu F, Kurita A. 2004. Effect of chronic stress and sleep deprivation on both flow-mediated dilation in the brachial artery and the intracellular magnesium level in humans. *Clin. Cardiol.* 27:223–27
96. Thiesse L, Rudzik F, Spiegel K, Leproult R, Pieren R, et al. 2018. Adverse impact of nocturnal transportation noise on glucose regulation in healthy young adults: effect of different noise scenarios. *Environ. Int.* 121:1011–23
97. Van Renterghem T, Botteldooren D. 2012. Focused study on the quiet side effect in dwellings highly exposed to road traffic noise. *Int. J. Environ. Res. Public Health* 9:4292–310
98. Vienneau D, Schindler C, Perez L, Probst-Hensch N, Röösli M. 2015. The relationship between transportation noise exposure and ischemic heart disease: a meta-analysis. *Environ. Res.* 138:372–80
99. Wang J, Yu W, Gao M, Zhang F, Gu C, et al. 2015. Impact of obstructive sleep apnea syndrome on endothelial function, arterial stiffening, and serum inflammatory markers: an updated meta-analysis and metaregression of 18 studies. *J. Am. Heart Assoc.* 4:e002454
100. Warby SC, Wendt SL, Welinder P, Munk EG, Carrillo O, et al. 2014. Sleep-spindle detection: crowdsourcing and evaluating performance of experts, non-experts and automated methods. *Nat. Methods* 11:385–92
101. WHO (World Health Organ.). 2009. *Night noise guidelines for Europe*. Rep., WHO Reg. Off. Eur., Copenhagen. **http://www.euro.who.int/__data/assets/pdf_file/0017/43316/E92845.pdf**
102. WHO (World Health Organ.). 2011. *Burden of disease from environmental noise—quantification of healthy life years lost in Europe*. Rep., WHO Reg. Off. Eur., Copenhagen

103. WHO (World Health Organ.). 2018. *Environmental noise guidelines for the European region*. Rep., WHO Reg. Off. Eur., Copenhagen. **http://www.euro.who.int/__data/assets/pdf_file/0008/383921/noise-guidelines-eng.pdf?ua=1**
104. Wilking M, Ndiaye M, Mukhtar H, Ahmad N. 2013. Circadian rhythm connections to oxidative stress: implications for human health. *Antioxid. Redox Signal.* 19:192–208
105. Wunderli JM, Pieren R, Habermacher M, Vienneau D, Cajochen C, et al. 2016. Intermittency ratio: a metric reflecting short-term temporal variations of transportation noise exposure. *J. Expo. Sci. Environ. Epidemiol.* 26:575–85
106. Xia N, Li H. 2018. Loneliness, social isolation, and cardiovascular health. *Antioxid. Redox Signal.* 28:837–51
107. Zare Sakhvidi MJ, Zare Sakhvidi F, Mehrparvar AH, Foraster M, Dadvand P. 2018. Association between noise exposure and diabetes: a systematic review and meta-analysis. *Environ. Res.* 166:647–57
108. Zeeb H, Hegewald J, Schubert M, Wagner M, Dröge P, et al. 2017. Traffic noise and hypertension—results from a large case-control study. *Environ. Res.* 157:110–17
109. Zweier JL, Chen C-A, Druhan LJ. 2011. S-glutathionylation reshapes our understanding of endothelial nitric oxide synthase uncoupling and nitric oxide/reactive oxygen species-mediated signaling. *Antioxid. Redox Signal.* 14:1769–75