

COMPENDIUM ON ENVIRONMENTAL IMPACTS ON CARDIOVASCULAR HEALTH AND BIOLOGY

Transportation Noise Pollution and Cardiovascular Health

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ABSTRACT: Epidemiological studies have found that transportation noise increases the risk for cardiovascular morbidity and mortality, with solid evidence for ischemic heart disease, heart failure, and stroke. According to the World Health Organization, at least 1.6 million healthy life years are lost annually from traffic-related noise in Western Europe. Traffic noise at night causes fragmentation and shortening of sleep, elevation of stress hormone levels, and increased oxidative stress in the vasculature and the brain. These factors can promote vascular (endothelial) dysfunction, inflammation, and arterial hypertension, thus elevating cardiovascular risk. The present review focusses on the indirect, nonauditory cardiovascular health effects of noise. We provide an updated overview of epidemiological research on the effects of transportation noise on cardiovascular risk factors and disease, and mechanistic insights based on the latest clinical and experimental studies and propose new risk markers to address noise-induced cardiovascular effects in the general population. We will discuss the potential effects of noise on vascular dysfunction, oxidative stress, and inflammation in humans and animals. We will elaborately explain the underlying pathomechanisms by alterations of gene networks, epigenetic pathways, circadian rhythm, signal transduction along the neuronal-cardiovascular axis, and metabolism. We will describe current and future noise mitigation strategies. Finally, we will conduct an overall evaluation of the status of the current evidence of noise as a significant cardiovascular risk factor.

Key Words: biological availability ■ blood pressure ■ monocytes ■ mortality, premature ■ nitric oxide

Extensive research has been conducted on adverse health impacts of air pollution and cardiovascular disease (CVD), and it is well-established that air pollution encompasses conditions such as acute myocardial infarction (MI), heart failure, arrhythmia, hypertension, and stroke (for review, see reference ¹). Recent studies have identified particulate matter with a diameter of ≤ 2.5 μm as a leading air pollutant contributing to ≈ 8.8 million annual excess deaths.² Surprisingly, much less attention has been given to another frequent environmental pollutant: transportation noise. This is somewhat puzzling, given that urban areas experience simultaneous exposure to high air pollution and noise levels.^{3–5} Noise is defined as unwanted and harmful sound and includes

transportation, occupational, leisure, residential, and industrial noise (Figure 1).⁹

In their 2020 report, the European Environment Agency highlighted that many people remain exposed to high road traffic noise levels.¹⁰ The European Environment Agency estimated that at least 20% of the population in the European Union (EU) resides in areas where transportation noise, mainly from roads, exceeds 55-dB L_{den} , though this number is considered underestimated, as exposure is mainly estimated in large agglomerations and among highways.¹⁰ According to the World Health Organization (WHO), adverse health impacts are likely at this noise level. Noise exposure at night is even more detrimental, and the WHO recommends that nocturnal

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Nonstandard Abbreviations and Acronyms	
CRP	C-reactive protein
CVD	cardiovascular disease
eNOS	endothelial nitric oxide synthase
EU	European Union
Foxo3	forkhead box protein 3
HR	hazard ratio
IHD	ischemic heart disease
MI	myocardial infarction
NADPH	nicotinamide adenine dinucleotide phosphate
NOX-2/gp91phox	nicotinamide adenine dinucleotide phosphate oxidase catalytic subunit 2
ROS	reactive oxygen species
RR	relative risk
WHO	World Health Organization
WHO ENG	Environmental Noise Guidelines for the European Region from the WHO
α1AMPK	α1 AMP-activated protein kinase

noise from road traffic does not exceed 45 dB(A) (L_{night}).¹¹ Estimations of the number of people exposed to transportation noise are also available outside of Europe. However, these estimations are often based on rather simple exposure models, likely resulting in an underestimation of the proportion exposed to noise; for example, the US Department of Transportation estimated that in 2018, 7.3% of the US population were exposed to road traffic noise levels above 50 dB $L_{aeq,24}$ (corresponding to a L_{den} of ≈53 dB).¹²

The global health burden arising from noise is substantial, mainly shown in calculations from the EU, as these calculations require valid information on the proportion of the population exposed to noise. Annually, in the EU, transportation noise is estimated to result in 12 000 premature deaths, 48 000 new cases of ischemic heart disease (IHD), 6.5 million people experiencing chronic sleep disturbances, and 22 million individuals enduring significant annoyance.¹³ The population's exposure to environmental noise is projected to increase due to urban expansion and growing demand for mobility.¹³ Projections indicate an apparent rise in the number of individuals exposed to road noise exceeding 55 dB(A) in L_{den} (day-evening-night level; Table S1) by 7.8% and railway noise by 11.8% within urban areas and 16.4% and 8.7%, respectively, outside urban areas by 2030.¹³ In contrast, the exposure to aircraft noise will remain unchanged inside and outside the metropolitan area.¹³

Babisch¹⁴ introduced the noise reaction model in which an indirect pathway plays a pivotal role in the development and progression of CVD. A key element of this model is the cognitive perception of noise, which triggers cortical activation and release of stress hormones (Figure 1). Over time, this can lead to the emergence of cardiovascular risk factors, such as diabetes, high cholesterol, and high blood pressure, ultimately manifesting as CVD, including conditions such as acute and chronic coronary syndrome, heart failure, persistent hypertension, arrhythmias, and stroke (for review, reference see⁸). Noise also disrupts sleep, daily activities, and communication, causing annoyance and reduced sleep quality and duration, potentially linked with an increased risk of CVD⁸ (Figure 1). The noise-induced activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system triggers the release of stress hormones such as cortisol and catecholamines.⁸ This, in turn, induces inflammation, leading to increased levels of IL (interleukin)-6, IL-1β, and proinflammatory monocytes, along with oxidative stress.⁶ Nighttime exposure to aircraft noise has even been linked to stress-induced cardiomyopathy, also known as Takotsubo syndrome.¹⁵ Stress responses can increase blood pressure, potentially impairing vascular function. This affects eNOS (endothelial nitric oxide synthase), increases oxidative stress, and reduces vascular nitric oxide bioavailability, ultimately causing endothelial dysfunction and rendering blood vessels more sensitive to stress-induced vasoconstriction (Figure 1).¹⁶

In this review, our primary focus is to explore the indirect, nonauditory impacts of transportation noise on cardiovascular health. We summarize epidemiological and clinical findings and mechanistic and experimental data. Additionally, we shed light on emerging indicators to better understand the cardiovascular consequences of noise in the general population. Mechanistic data related to the adverse health effects of noise focus on impaired vascular function, oxidative stress, and inflammation. Pathomechanisms also encompass alterations in gene networks, epigenetic pathways, circadian rhythms, signal transmission within the neuronal-cardiovascular connection, and metabolic processes. Finally, we provide an overview of the most promising strategies for mitigating noise-related health issues and assess the existing body of evidence about noise as a risk factor for cardiovascular health.

EPIDEMIOLOGICAL EVIDENCE

Transportation Noise and CVD and Death

Over the past years, there has been a growing body of evidence on the effects of environmental noise on cardiovascular health.¹⁷ The meta-analyses commissioned by the WHO that were published as part of the Environmental Noise Guidelines for the European Region from the WHO

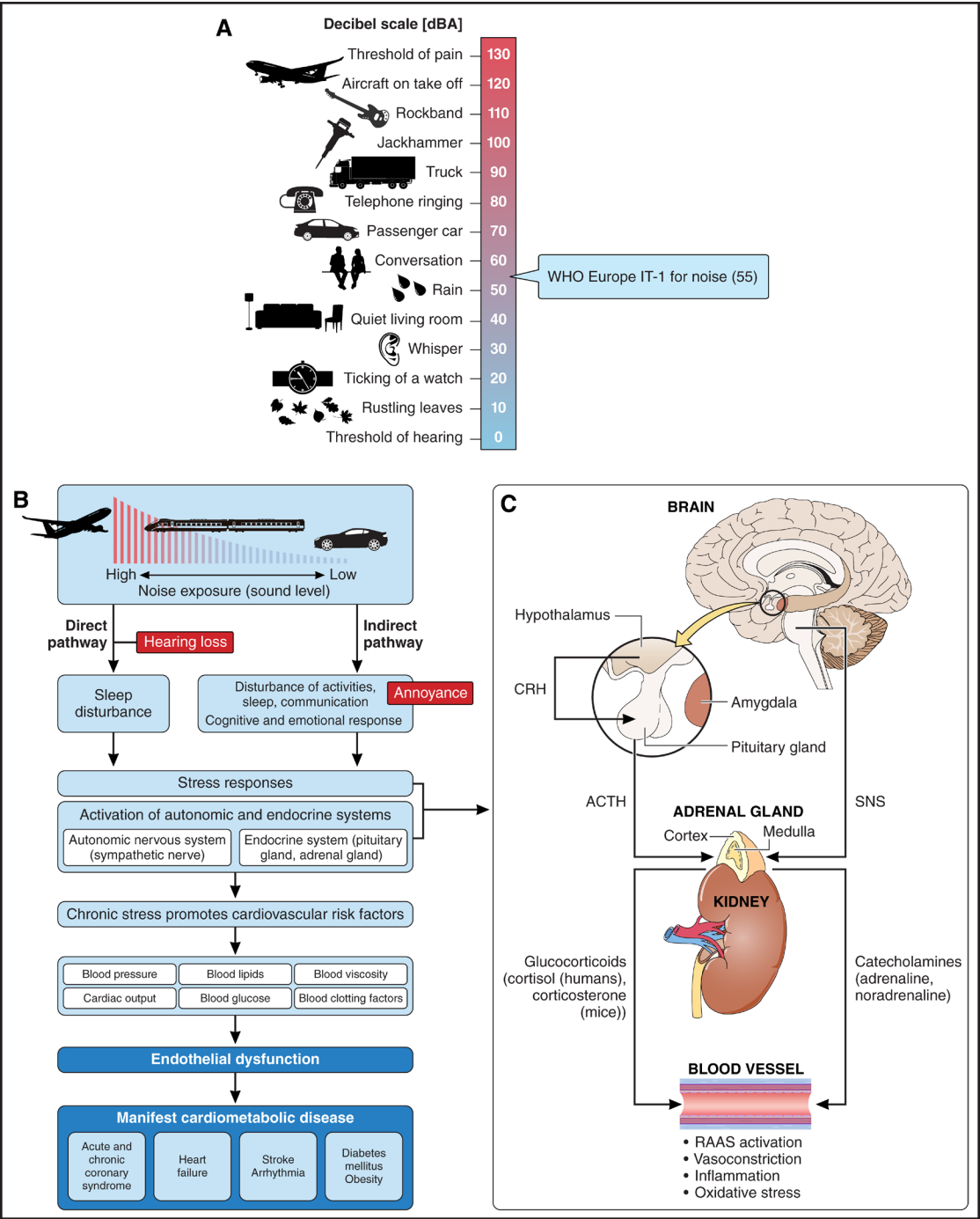


Figure 1. Sound pressure levels of environmental noise sources, noise stress concept and adverse health consequences in humans. **A**, Sound pressure levels of different noise sources.⁶ **B**, Noise reaction model for noise exposure's direct (auditory) and indirect (nonauditory) effects.⁷ **C**, Neuronal activation (arousals) induced by noise triggers signaling via the hypothalamic-pituitary-adrenal axis and sympathetic nervous system (SNS). This leads to the release of corticotropin-releasing hormone (CRH) from the hypothalamus into the pituitary gland, which stimulates the release of adrenocorticotrophic hormone (ACTH) into the blood. ACTH induces the production of glucocorticoids by the adrenal cortex, and the activation of the SNS stimulates the production of catecholamines by the adrenal medulla. The release of glucocorticoids and catecholamines, in turn, leads to the activation of other neurohormones and pathways, such as the renin-angiotensin-aldosterone system, and increased inflammation and oxidative stress. **A** was reprinted from Munzel et al⁶ with permission. Copyright ©2018, the authors. **B** and **C** were adapted from Munzel et al⁸ with permission. Copyright ©2021, Springer Nature Limited. Illustration credit: Sceyence Studios.

(WHO ENG)¹⁸ included studies published until 2015. We identified subsequent studies in a 2023 Umbrella+review, for which we combined results from the newest high-quality systematic review with original studies that were published after the corresponding review. In case, no systematic review was identified; we considered all studies

published between 2015 and Medio 2023 together with the WHO ENG.¹⁹ We only included high-quality systematic reviews, which we identified based on the quality of the literature search, the risk of bias assessment, and the methodology of the meta-analysis using an adopted AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews, version 2).²⁰ Eligible original studies had to apply reliable noise exposure assessment methods and account for the most relevant confounders. For mortality and incident CVDs, only cohort studies were included, whereas for prevalent hypertension, also case-control and cross-sectional studies were included if they were population-based, had a large sample size, and established methods for outcome assessment (for details, see reference ¹⁹).

Based on the Umbrella+ review, we conducted meta-analyses to obtain up-to-date exposure-response functions for CVD and mortality. An Umbrella+ review summarizes results from the newest high-quality systematic reviews combined with original studies published after the corresponding review. A summary of the Umbrella+ CVD results is given in the following (Figure 2).

Cardiovascular Mortality

In the systematic literature search for the Umbrella+ review, we identified 61 potentially eligible cardiovascular and IHD mortality papers. Thereof, 12 prospective cohort studies on road, railway, and aircraft noise were eligible for meta-analysis (Table S2). Figure S1 shows the results of the meta-analysis. Based on 9 studies, the pooled effect estimate per 10 dB(A) of road traffic noise was 1.05 (95% CI, 1.02–1.07).¹⁹ For railway and aircraft noise, only 2 studies were available for each exposure, suggesting either no or minimal effect of these 2 exposures on cardiovascular mortality (Figure S1).

In support of the effect of noise on CVD mortality, a recent case-crossover study from Switzerland found that short-term exposure to aircraft noise was associated with CVD mortality.²² More specifically, the study showed that nighttime aircraft noise of 40 to 50 and >50 dB, 2 hours preceding a CVD death, was associated with odds ratios (95% CI) of, respectively, 1.33 (1.05–1.67) and 1.44 (1.03–2.04) compared with exposures below 20 dB. This suggests that in addition to the chronic effects of exposure to noise on the risk of CVD, acute noise exposure may trigger CVD death.

Ischemic Heart Disease

A systematic review published as part of the WHO ENG¹⁸ assessed the association between transportation noise and incidence of IHD and found a relative risk (RR) of 1.08 (95% CI, 1.01–1.15) per 10-dB(A) increase in L_{den} based on 3 cohort and 4 case-control studies.²¹ The working group rated the evidence for an association to be high. Only ecological or cross-sectional studies were identified for railway and aircraft noise, which led to a low certainty of evidence.

Since then, many studies have been published investigating noise and IHD incidence. The most recent studies include a pooled analysis of Danish and Swedish cohorts²³ and a nationwide study with >2.5 million participants.²⁴ Both studies found road traffic noise to increase IHD incidence with hazard ratios (HRs) of 1.03 (95% CI, 1.00–1.05) and 1.05 (95% CI, 1.04–1.06), respectively. For railway noise, however, the results are inconsistent.^{23,24}

We found that in a meta-analysis combining the WHO ENG review²¹ with 3 new cohort studies and the pooled Scandinavian cohort (Table S3), a 10-dB(A) increase in road traffic noise was associated an RR of 1.04 (95% CI,

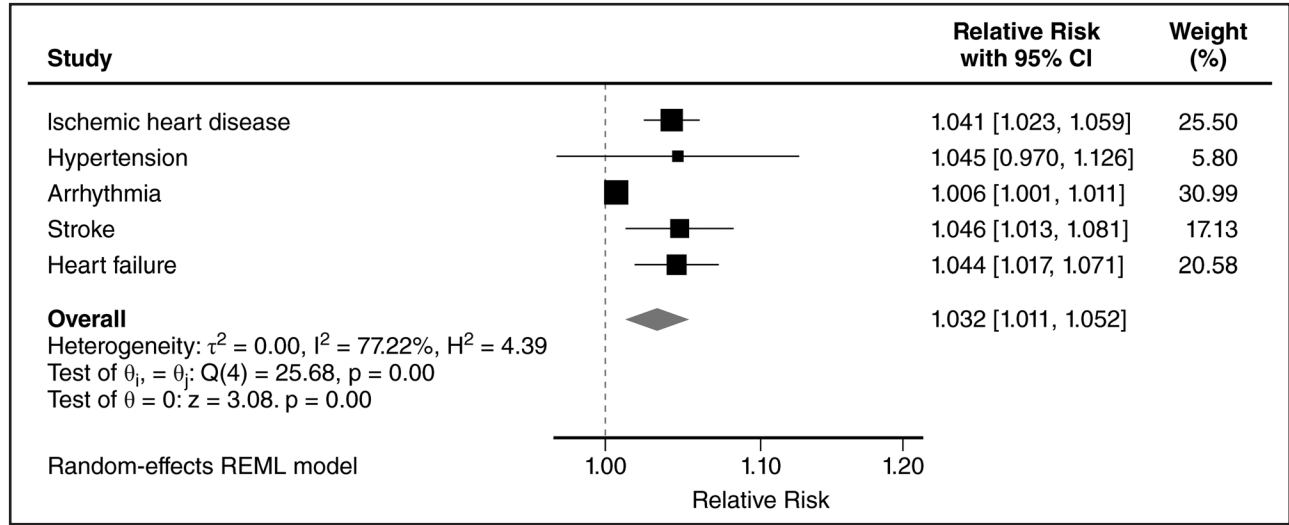


Figure 2. Relative risks obtained in meta-analyses of an Umbrella+ review from 2024 estimating the association between road traffic noise and cardiovascular disease.¹⁹ In the Umbrella+ review, we conducted a systematic search for the period 2015 until Medio 2023 and combined with all studies identified until 2015 in a systematic search conducted by a World Health Organization expert group.²¹ Relative risks refer to a 10-dB increase in L_{den} . REML indicates restricted maximum likelihood. Illustration credit: Sceyence Studios.

1.02–1.06) for IHD incidence (Figure 2).¹⁹ Corresponding RRs (95% CI) for aircraft and railway noise were 1.01 (0.99–1.03) and 1.00 (0.93–1.06), respectively. All studies in the meta-analysis on road traffic noise are based on European cohorts, including the seven studies in the WHO ENG review.²¹ To increase generalizability, conducting noise studies outside Europe is important. In 2023, an individual-level US study, based on the Nurses' Health study, found anthropogenic noise associated with a higher risk of incident coronary heart disease.²⁵ However, as discussed in an invited perspective, the method for estimating noise in the US study differed markedly from the methods used in European studies,²⁶ making direct comparison problematic. While European studies focus on estimating source-specific noise at address-level precision using sound propagation models for road traffic noise based on traffic data from all roads (eg, traffic volumes and speed) combined with building infrastructure and topography, the US study relied on a geo-spatial model based on noise measurements from 492 monitoring stations across the United States, combined with spatial data such as population density. The US model cannot estimate source-specific noise and instead provides an estimate of total anthropogenic noise, which is a limitation for evidence-based noise policy. Also, noise is estimated in relatively low resolution (270×270 m),²⁵ which is likely to cause attenuation of the association between noise and CVD, especially in urban settings.²⁷

Stroke

In the WHO ENG, only 1 cohort study on road traffic noise and incident stroke was available, finding an HR of 1.14 (95% CI, 1.03–1.25).¹⁸ Certainty of evidence was, thus, assessed by the WHO working group to be moderate. For railway and aircraft noise, no cohort studies were identified. Since then, 9 studies on stroke have been published, mostly indicating positive associations between road traffic noise and risks close to unity for rail and aircraft noise. Among others, a pooled analysis including multiple cohorts from Denmark and Sweden resulted in an increased risk with an HR of 1.06 (95% CI, 1.03–1.08) per 10 dB(A) higher road traffic noise.²⁸

In the Umbrella+ review, we found that based on 6 cohort studies (Table S3), road traffic noise increased the risk of incident stroke, with an RR per 10 dB(A) of 1.05 (95% CI, 1.01–1.08).¹⁹ In contrast, aircraft and railway noise, both based on 2 studies, was not associated with stroke, with pooled RR (95% CI) of 1.00 (0.88–1.13) and 0.97 (0.96–0.98), respectively.

Heart Failure

The WHO ENG¹⁸ did not address the effects of environmental noise on the risk of heart failure. In 2023, a meta-analysis found road traffic noise to be associated with a 5% higher risk per 10 dB.²⁹ Presently, there are 6 longitudinal studies that addressed this association, all showing

positive associations, with RRs between 1.01 and 1.09 per 10-dB(A) increase in road traffic noise (Table S3). In an updated meta-analysis, we found road traffic noise to increase the risk of heart failure, with an RR of 1.04 (95% CI, 1.02–1.07) per 10-dB(A) increase (Figure 2).¹⁹ One study assessing railway noise indicated no association.²⁴ For aircraft noise, a German study³⁰ showed a decrease in risk, whereas a Danish nationwide study presented a positive association with an RR of 1.06.²⁴ The pooled RR for railway and aircraft noise, derived from 2 studies each, was 1.01 (95% CI, 1.00–1.04) and 1.02 (95% CI, 0.93–1.11) per 10-dB(A) L_{den} , respectively.

Arrhythmia

Although a few reviews have addressed the association between noise and arrhythmia, no meta-analyses have been conducted. Furthermore, only a few cohort studies exist. These studies include a Danish nationwide cohort study³¹ with over 3.5 million participants of whom 269 756 developed atrial fibrillation. This study reported weak positive associations with road, railway, and aircraft noise, with risk increases of 1% to 2% per 10 dB(A).

In an updated meta-analysis for road traffic noise based on 3 cohort studies, we found an RR of 1.01 (95% CI, 1.00–1.01) per 10 dB(A), whereas the pooled RR for aircraft noise, which was based on 2 studies, was 1.21 (95% CI, 0.70–2.08) per 10 dB(A).¹⁹ Only one study provided an estimate for railway noise, which was 1.02 (95% CI, 1.01–1.03) per 10 dB(A).

Conclusions on Cardiovascular Incidence Studies

Based on the Umbrella+ review, we conclude that evidence exists for an association between road traffic noise and IHD, stroke, and heart failure. For all cardiovascular diagnoses combined, the risk increased by 3.2% (95% CI, 1.1%–5.2%) per 10 dB(A) higher road traffic noise (L_{den} ; Figure 2). Importantly, this evidence would be further strengthened if intervention studies could demonstrate a reduction in the risk of CVD after the implementation of noise mitigation. Unfortunately, no high-quality intervention studies on environmental noise and the risk of CVD have been published. Associations tended to be less pronounced for railway and aircraft noise. It is conceivable that noise from railways and aircraft is often masked by the substantially more prevalent road traffic noise, and this may explain why the exposure-response association for these 2 sources may not be as accurately estimated as for road traffic.

Lower Effect Threshold of Noise

The lower effect threshold of noise is defined as the level below which no health effects of noise are expected. This threshold has not been determined with certainty. Also, the threshold likely varies between sources of noise. Different noise recommendation limits exist across the world. For example, the EU currently incorporates a noise

mapping threshold of 55-dB(A) L_{den} as part of the European Noise Directive. In contrast, the WHO, in their 2018 guidelines, recommended a 53-dB(A) threshold for road traffic noise (L_{den}).¹¹

Recently, several studies based on large cohorts have investigated the shape of the exposure-response function for transportation noise in relation to various outcomes with large statistical power across the entire exposure span, starting from around 35 to 40 dB(A; approximately background level of noise) until 80 to 85 dB(A).^{23,24,28,32,33} Many of these studies suggest that the effects of noise on morbidity and mortality start already from 35 to 40 dB(A), for example, for stroke,^{28,32} diabetes,³⁴ and cardiovascular mortality.^{33,35} For IHD, studies have suggested a threshold between 50 and 55 dB(A).^{23,24}

As illustrated in the Table, correct assignment of the effect threshold level is highly important when performing a health impact assessment, an essential tool for decision-makers prioritizing noise prevention. This table shows results from health impact assessments concerning CVD mortality and incident IHD for Denmark and Switzerland using 4 potential lower effect threshold scenarios for road traffic noise. These calculations are possible because researchers in Denmark and Switzerland have performed estimations of road traffic noise for the entire population throughout the exposure range.^{27,38} We observed that the calculated numbers of IHD and CVD deaths due to road traffic noise were 3 to 4 times higher when using 45 dB(A) as a lower effect threshold than 55 dB(A), highlighting the importance of identifying the correct effect threshold for noise.

Effects of Noise on Cardiovascular Risk Factors

Cardiovascular Effects of Noise—Short Introduction and Historic Overview

The concept that nonauditory effects of noise contribute substantially to health consequences was suggested in a 1970 monography.³⁹ The monography described results

showing that acute noise exposure had cardiovascular effects, for example, a study establishing that noise exposure led to constricting peripheral blood vessels in individuals engaged in physical exercise.⁴⁰ Also, a study showed that exposure to noise or music elicited varying hemodynamic responses, including cardiac output and minute flow, and the authors concluded that the intensity of the sound, rather than its aversive (noise) or pleasurable (music) qualities, governed the somatic responses.⁴¹

Among 1005 German industrial workers, it was observed in 1968 that workers in noisy industries exhibited more pronounced peripheral circulation problems, heart issues, and equilibrium disturbances than workers in less noisy industries.⁴² In 1993, the Speedwell study reported significant associations between road traffic noise and risk factors for IHD. These included increases in total triglycerides, platelet count, plasma viscosity, glucose levels, and systolic and diastolic blood pressures.⁴³ Moreover, higher noise levels were significantly linked to elevated systolic and diastolic blood pressures and heart rate.⁴⁴ Later, a study found that nighttime transportation noise led to more pronounced increases in blood pressure compared with daytime exposure.⁴⁵ It was suggested that repeated nighttime autonomic arousals may disrupt the natural nocturnal decline in blood pressure.⁴⁶ Also, in workers exposed to occupational noise exceeding 80-dB(A) L_{aeq} , a significant increase in systolic and diastolic blood pressures was observed along with elevated levels of glutathione peroxidase and DNA damage compared with office workers exposed to between 40- and 50-dB(A) L_{aeq} .⁴⁷

Arterial Hypertension

A 2021 review assessed hypertension in relation to transportation noise and derived pooled estimates stratified by noise source and study type.⁴⁸ While the meta-analysis for road traffic noise showed no association between cohort and case-control studies, an increased odds ratio of 9% per 10 dB(A) was seen in cross-sectional studies. No associations were observed between

Table. Estimated Number of People Who Died and Had an Incident IHD Due to Exposure to Road Traffic Noise in Denmark and Switzerland.

Lower effect threshold (L_{den}), dB	Denmark (5.75 million)		Switzerland (8.48 million)	
	Cardiovascular mortality*	IHD incidence†	Cardiovascular mortality*	IHD incidence†
55	206	256	166	291
53	270	336	234	412
50	385	478	371	651
45	616	764	688	1207

The lower effect threshold of road traffic noise, corresponding the level below which no health effects of noise are expected, is presently unknown, and, therefore, numbers are estimated for 4 lower harmful level scenarios. For both Denmark and Switzerland, numbers are estimated using road traffic noise calculated for nationwide epidemiological projects estimating noise from 35 db and up.^{36,37} CVD indicates cardiovascular disease; IHD, ischemic heart disease; and PAF, population attributable fraction.

*PAF was estimated using a relative risk of 1.045 for CVD mortality and the proportion of people in different noise categories. Number of people with CVD mortality is calculated as PAF*CVD mortality in Denmark (n=12 455; 2017) and Switzerland (n=19 645; 2021), respectively.

†PAF was estimated using a relative risk of 1.041 for IHD and the proportion of people in different noise categories. Number of people with incident IHD was calculated as PAF*IHD in Denmark (n=16 984; 2017) and Switzerland (n=37 878; 2021), respectively.

aircraft and railway noise. Since then, 3 studies have been published on aircraft noise and the risk of hypertension, of which 2 studies were based on populations from the United States, showing that comparing individuals exposed to above 45 dB(A) versus those below 45 dB(A; day-night average) resulted in HRs (95% CI) of 1.00 (0.93–1.08)⁴⁹ and 1.03 (0.99–1.07).⁵⁰ In contrast, a French study found aircraft noise to increase the risk of hypertension, with an HR of 1.36 (1.02–1.82) per 10 dB(A) higher L_{den} .⁵¹

In a meta-analysis pooling of the risk estimates from cohort and cross-sectional studies, we found an RR of 1.04 (95% CI, 0.97–1.13) per 10-dB(A) road traffic noise and 1.03 (95% CI, 1.01–1.05) per 10-dB(A) aircraft noise.^{19,48} No studies were identified for railway noise. This suggests that transportation noise may increase the risk of hypertension though more longitudinal studies are needed to investigate this further.

Diabetes and Obesity

Type 2 diabetes and obesity are frequent comorbidities in patients with CVD,^{52,53} and adverse effects of noise on these 2 conditions may, therefore, contribute to the link between noise and CVD. Several recent cohort studies have consistently linked transportation noise, especially from road traffic, with a higher risk of diabetes.^{34,54–60} A meta-analysis from 2023 found that a 10 dB(A) higher road traffic noise was associated with an RR for diabetes of 1.06 (95% CI, 1.03–1.09).⁶¹ Interestingly, 2 studies have investigated the effects of road traffic noise at both the most exposed façade (standard noise measure) and the least exposed façade, considered to be a proxy for bedroom noise exposure, as people often chose to sleep in a room facing away from a busy street.^{34,62} These 2 studies found more potent effects of noise at the least exposed façade than the most exposed façade, suggesting that for diabetes, the effects of noise on sleep are a potential mechanism. Furthermore, noise-induced endothelial dysfunction is suggested to contribute to the adverse metabolic effects of noise.⁶³ In line with this, a recent study demonstrated that endothelial dysfunction can predict the onset and progression of type 2 diabetes.⁶⁴

Few prospective cohort studies have investigated the effects of exposure to transportation noise on the risk of developing adiposity.^{65–70} The measures of adiposity varied across the studies, with 4 studies investigating effects on weight gain/body mass index,^{65,66,68–70} 2 studies on waist circumference changes,^{65,66} and 2 studies on the risk of obesity/overweight.^{66,67} While evidence is still emerging, the currently available research suggests an association between exposure to road traffic noise and an increased risk of adiposity. Interestingly, this was shown in both child cohorts,^{69,70} a pregnancy cohort,⁶⁸ and adult and elderly populations,^{65–67} suggesting that exposure to road traffic noise may affect the risk of adiposity throughout life. It is, thus, likely that adiposity is on the mechanistic pathway between noise and cardiometabolic disease, and epidemiological studies should,

therefore, avoid adjustment for body mass index, as this could result in overadjustment and underestimation of actual effects.

Mental Health

Major depression and other psychological factors are acknowledged risk factors for CVD,⁷¹ and the effects of transportation noise on mental health could, therefore, be an essential mediator in explaining the effects of transportation noise on CVD risk. A 2020 meta-analysis found that road traffic and aircraft noise were associated with a higher risk of depression, with RRs (95% CI) per 10 dB(A) of 1.03 (0.99–1.06) and 1.12 (1.02–1.23), respectively.⁷² Since this meta-analysis, new longitudinal studies have supported that road traffic noise may increase the risk of depression, poorer mental health-being,^{73,74} and suicide.⁷⁵ One study, furthermore, suggested that the effects of road traffic noise on depression seemed to be partly mediated by annoyance toward noise,⁷³ supported by a prospective study showing that noise annoyance at baseline was associated with risk of depression and anxiety symptoms 5 years later.⁷⁶ The observed linkage between transportation noise and depression needs confirmation in more high-quality prospective studies.

Lifestyle Habits

A few studies have investigated whether road traffic noise is associated with unhealthy lifestyle habits,^{77–79} which seems plausible as noise is believed to exert its harmful effects through 2 main pathways associated with lifestyle changes, namely, stress and sleep disturbance. Effects of noise on leisure-time physical activity have been studied in 2 studies, investigating the effects of estimated residential road traffic noise and self-reported transportation noise annoyance.^{77,78} Both studies suggested that road traffic noise might have a negative impact on physical activity.⁷⁸ One study investigated the effects of road traffic noise on smoking and alcohol habits.⁷⁹ Although the study showed that road traffic noise was positively associated with smoking and alcohol intake in cross-sectional analyses, longitudinal analyses showed no associations with lifestyle changes. New, well-designed cohort studies are highly necessary to investigate whether the effect of noise on lifestyle is an important mediator on the pathway between noise and CVD. If physical activity, smoking, and alcohol are found in future studies to be on the biological pathway between noise and cardiometabolic disease, then adjustment for these lifestyle variables in epidemiological studies could result in overadjustment.

Sleep Disturbance

The American Academy of Sleep Medicine and Sleep Research Society recommends that adults obtain 7 to 9 hours of high-quality sleep to promote well-being and health.⁸⁰ Conversely, sleep that is disturbed or too short has been associated with increased mortality and several

adverse health outcomes, first and foremost CVD.⁸¹ In 2022, the American Heart Association added sleep to their list of lifestyle factors with critical importance for cardiovascular health. Noise disrupts sleep by causing intermittent awakenings or brief arousals, reducing continuity.⁸² Consequently, sleep will be shorter and lighter with less time spent in deep and rapid eye movement sleep, which is crucial for sleep recovery. This is evidenced by increased daytime sleepiness and decreased performance after noisy nights.⁹ Even when sleep stages are unaffected, noise can increase the number and intensity of autonomic arousals, negatively affecting metabolic and cardiovascular function.^{82,83} In addition to the sound level, the sleep-disturbing properties depend not only on other noise characteristics such as rise time and frequency content but also on the meaning of the sound to the recipient.⁸²

Epidemiological studies suggest that nighttime noise exposure has a more significant impact on long-term health outcomes than daytime noise exposure, likely also because people are more consistently at home during the night.⁸⁴ Studies have shown that even a single night of exposure to rail or aircraft noise can impair flow-mediated dilation of the brachial artery, a finding replicated in individuals with or at high risk for coronary artery disease.^{85,86} Noise also prevents blood pressure from dipping during the night,⁴⁶ with plausible long-term effects on CVD risk. Analysis of blood proteins showed that noise exposure induces changes indicative of a prothrombotic and pro-inflammatory state, providing a biological basis for the increased risks of CVD and other diseases, such as neurodegenerative disease, obesity, diabetes, and breast and colon cancer.⁸⁶ In one animal study, adverse effects on blood vessels and composition were primarily observed if the noise exposure was intermittent during the sleep phase, again highlighting the importance of undisturbed sleep for health.⁸⁷ More experimental studies are needed, which focus on the direct associations between noise-induced sleep disturbance and biomarker changes. This will strengthen the assumption that sleep disturbance is on the causal pathway between nighttime noise exposure and CVD. A recent retrospective case-crossover study at Zurich airport revealed an association between aircraft noise exposure levels in the 2 hours before an event and cardiovascular mortality.²² Thus, nocturnal noise exposure may contribute to physiological changes that elevate CVD risk and trigger fatal events through physiological arousal.

Noise Annoyance

Noise annoyance is a psychological response to unwanted or disturbing sounds, encompassing cognitive, emotional, and behavioral reactions. Globally, road traffic noise is the primary source of noise annoyance, while neighborhood noise is another substantial but understudied contributor. ISO standards provide a framework for assessing noise annoyance through population surveys, utilizing the percentage of highly annoyed metric.^{88,89}

Acoustic characteristics of noise exposure, such as intensity, frequency, complexity, and duration, do not solely determine noise annoyance reactions. They are significantly influenced by personal, social, and situational factors, encompassing age, sex, health status, noise sensitivity, attitude toward noise, socioeconomic status, public perception, perceived stress, and coping abilities.⁹⁰ In the WHO ENG, exposure-response relationships for road, railway, and aircraft noise estimated in meta-analyses, ranked aircraft noise as the most annoying.⁹¹ Recent trends showed increased annoyance for aircraft and railway noise while remaining relatively stable for road traffic noise, necessitating further investigation into these variations.^{92,93}

Noise annoyance can be an early indicator of more severe health risks due to its rapid onset compared with physical illnesses. Historically, annoyance has been a critical indicator for shaping noise policies, with noise protection limit values partially based on exposure-response functions for annoyance. WHO recommends noise level reductions to protect against adverse health effects, primarily informed by noise annoyance surveys. However, evolving epidemiological studies are focusing on cardiometabolic health outcomes.⁹⁴

MECHANISTIC NOISE STUDIES IN HUMANS

Translational Studies of Transportation Noise on Endothelial Function and Oxidative Stress Markers in Humans

Through a series of field investigations (studies performed in the home of the subject), the adverse effects of nighttime aircraft and railway noise on vascular (endothelial) function, sleep quality, stress hormone release, and inflammation markers, both in healthy individuals and patients with CVD, were established.^{85,95} Noise recorded in a bedroom near the Düsseldorf airport was played back (30 or 60 times per night; noise30 and noise60) on a standard portable audio system with a fixed speaker position relative to the head of the subject.

These studies revealed that in healthy subjects, nighttime exposure to aircraft noise with an equivalent sound level of 46.3 dB(A) and a peak level of 60 dB(A) for 1 night caused decreased sleep quality, elevated levels of adrenaline, endothelial dysfunction (impaired flow-mediated dilation, a subclinical marker for atherosclerosis), and a reduction in pulse transit time, indicating sympathetic activation (Figure 3).⁹⁵ Notably, the acute administration of vitamin C of 2 g improved endothelial dysfunction 2 hours after administration, indicating the involvement of reactive oxygen species (ROS) in causing vascular dysfunction. Interestingly, a priming effect of aircraft noise on endothelial function was observed, that is, previous exposure to Noise30 caused Noise60 to

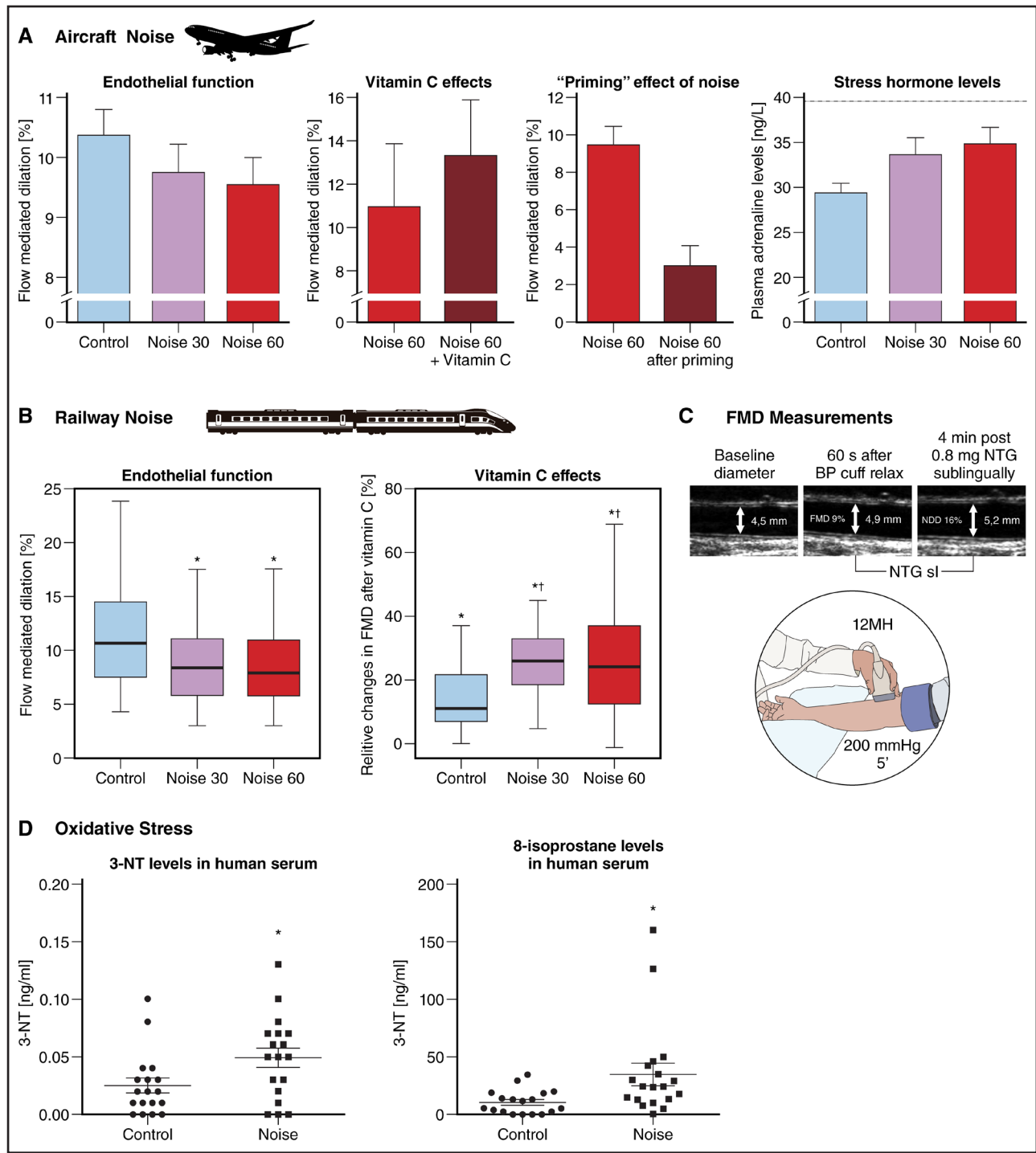


Figure 3. Key effects of noise observed in human field studies.
A, Effects of 30 and 60 aircraft noise events on flow-mediated dilation (FMD) of the brachial artery (noise 30 and 60) of 70 healthy subjects. Vitamin C effects were assessed in a subgroup of the cohort. A priming effect of aircraft noise on endothelial function was observed, that is, previous exposure to Noise30 caused Noise60 to have a significantly stronger reduction of flow-mediated dilation.⁹⁵ Serum adrenaline levels also increased significantly. **B**, Effects of 30 and 60 railway noise events on flow-mediated brachial artery dilation in 70 healthy subjects. Vitamin C effects were assessed in a subgroup.⁹⁶ **C**, Methodology of FMD. **D**, Effects of aircraft noise on oxidative stress markers (3-nitrotyrosine [3-NT] and 8-isoprostane) in serum that was measured in the samples of the aircraft noise study and published in reference⁸⁷. Adapted from Kroller-Schon et al⁸⁷ with permission. Copyright ©2018, Oxford University Press. Illustration credit: Sceyence Studios.

have a significantly larger adverse effect on endothelial function. These data demonstrate that aircraft noise can affect endothelial function and suggest that rather than habituation, prior noise exposure seems to amplify the negative effect of noise on endothelial function. Further support for the oxidative stress concept was established

by the demonstration of a significant increase in oxidative stress marker 3-nitrotyrosine and 8-isoprostane serum levels in response to aircraft noise exposure (Figure 3).⁸⁷

The adverse effects of aircraft noise on endothelial function were more pronounced in patients with established coronary artery disease, suggesting that an already compromised endothelium is more susceptible to further deterioration.⁸⁵ Similar investigations were conducted in healthy subjects exposed to either 30 (Noise30) or 60 train events (Noise60) during the nighttime, with L_{aeq} levels ranging from 33 to 54 dB(A) for 1 night (Figure 3).⁹⁶ This nocturnal exposure decreased sleep quality and impaired the brachial artery's flow-mediated dilation. Once again, acute challenges with vitamin C significantly ameliorated railway noise-induced endothelial dysfunction. In-depth proteomic analysis identified significant impacts on plasma proteins involved in redox, prothrombotic, proinflammatory, and fibrotic pathways compared with controls.⁹⁶

We have, furthermore, explored the influence of nighttime noise event loudness and frequency on endothelial function by exposing patients with established coronary artery disease to 2 nighttime aircraft noise scenarios, with comparable mean sound pressure levels: 1 with loud and infrequent noise events and 1 with less loud but more frequent noise events (equivalent sound level values of 37 dB[A] for control and 45 dB[A] for noise exposure for 1 night).⁹⁷ Both scenarios resulted in similar worsening of endothelial function. For the first time, we also observed a diastolic heart dysfunction (an increase in the E/E' ratio) as indicated by serial echocardiography. An exploratory protein analysis through proximity extension assay revealed significant decreases in 3 biomarkers (folistatin, glyoxalase I, and ACE-2 [angiotensin-converting enzyme 2]) associated with regulating heart function, oxidative stress, inflammation, and fibrosis.⁹⁷

Noise Causes Epigenetic Changes and an Adverse Impact on the Immune System

Cross-sectional cohort studies have found that exposure to transportation noise can impact the immune system. Two studies observed noise to increase levels of IL-12 and high-sensitivity CRP (C-reactive protein) while decreasing natural killer cell populations and activity^{98,99} although these results are not consistently uniform across all studies.⁸³ Furthermore, alterations in the immune system have been linked to elevated circulating cortisol levels and heightened noise sensitivity.^{98,99} Higher cortisol levels may be also related to nocturnal noise exposure and impaired circadian rhythm.^{100,101} Interestingly, a study based on the Swiss SAPALDIA cohort (Study on Air Pollution And Lung Disease In Adults) showed that long-term exposure to transportation noise and air pollution led to distinct and shared DNA methylation patterns, with enrichments in pathways related to inflammation (eg, CRP), cellular development, and immune responses.¹⁰² Based on the same

cohort, chronic exposure to nocturnal intermittent train or road traffic noise was suggested to increase arterial stiffness (reflecting endothelial dysfunction), as determined by pulse wave velocity.¹⁰³ This finding is supported by a German cohort study, showing that long-term exposure to nighttime road traffic noise was associated with subclinical atherosclerosis, especially in participants with early arterial calcification.^{104,105} Thus, in summary, these findings offer pathophysiological and molecular evidence from human studies, shedding light on the observed effects of transportation noise on incident CVD. Notably, the results from these human studies, including stress pathways, inflammation, oxidative stress, parameters of arterial stiffness, and endothelial/cardiac dysfunction, align with mechanistic data derived from animal studies (see subsequent sections).

MECHANISTIC NOISE STUDIES IN ANIMALS

Noise Causes Vascular Dysfunction, Oxidative Stress, and Inflammation

We developed a novel animal model to study the molecular mechanisms underlying noise-induced endothelial dysfunction. This involved exposing mice to continuous aircraft noise (with a constant equivalent sound level of 72 dB[A] and peak levels of 85 dB[A] for 24 hours a day, for 1, 2, and 4 days).¹⁶ This exposure significantly increased stress hormones, blood pressure, endothelial dysfunction, and oxidative stress in both vascular and cerebral systems, primarily from phagocytic NOX-2 (nicotinamide adenine dinucleotide phosphate (NADPH) oxidase catalytic subunit 2) and secondary to inflammation due to infiltrating immune cells, which was associated with diminished endothelial nitric oxide bioavailability, increased vascular superoxide, enhanced endothelin-1 expression, and sensitivity to vasoconstrictors.^{16,87} Importantly, endothelial dysfunction was associated with an upregulation rather than a downregulation of the eNOS. Further studies revealed that eNOS was uncoupled due to enhanced S-glutathionylation of eNOS, an established mechanism of eNOS uncoupling in the aorta.¹⁰⁶ When mice were exposed to white noise under similar conditions (comparable exposure time and mean sound pressure level), they did not exhibit these cardiovascular side effects. This suggests that it is not merely the sound pressure level itself, but rather the characteristics of the noise, such as frequency or noise pattern, which play a determining role in exerting cardiovascular damage.¹⁶ In addition, noise with a mean sound pressure level of 72 dB(A) for 4-day-induced oxidative DNA damage and enhanced NOX-2 expression in C57BL/6 mice.¹⁰⁷ In *Ogg1*^{-/-} (8-oxoguanine glycosylase) mice (DNA-repair deficient *Ogg1* knockout mice), we observed additive effects of noise on the degree of oxidative burst in blood leukocytes and other oxidative stress and inflammation markers.

To answer the question of whether microvascular endothelial/vascular dysfunction occurs in response to noise and whether there is a connection to inflammation, control mice and mice with genetic deletion of the phagocytic NADPH oxidase catalytic subunit (gp91phox or NOX-2) were exposed to aircraft noise for 4 days. In vivo fluorescence microscopy established a higher number of leukocytes adhering to the vasculature in noise-exposed wild-type mice. Microvascular diameter, red blood cell velocity, and segmental blood flow were decreased by noise exposure, indicating microvascular constriction. All adverse effects on functional parameters were normalized or improved in noise-exposed *gp91phox*^{-/-} mice. Noise exposure also induced substantial endothelial dysfunction in cerebral microvessels, associated with higher oxidative stress burden and inflammation, demonstrating a link between a proinflammatory phenotype of plasma, activation of circulating leukocytes, and microvascular dysfunction. Again, the phagocytic NADPH oxidase was identified as a central player in the underlying pathophysiological mechanisms.¹⁰⁸

Particularly interesting is that the molecular mechanisms underlying vascular dysfunction in response to continuous and intermittent (nighttime) aircraft noise closely resemble the mechanisms through which traditional cardiovascular risk factors, such as diabetes,¹⁰⁹ arterial hypertension,¹¹⁰ and smoking,¹¹¹ induce endothelial and vascular dysfunction. This suggests that noise-induced stress and preexisting cardiovascular risk factors may accelerate vascular and cerebral atherosclerosis and neurodegenerative diseases due to shared molecular pathomechanisms. In line with this, we noted that the adverse cardiovascular effects of aircraft noise were exacerbated in mice with preexisting arterial hypertension (angiotensin-II infused animals, exposed to a continuous equivalent sound level of 72 dB[A] and peak levels of 85 dB[A] for 24 hours a day for seven days).¹¹² This phenomenon was primarily driven by increased blood pressure, vascular inflammation, and oxidative stress. Noise further potentiated neuroinflammation and cerebral oxidative stress in hypertensive animals.¹¹²

Noise Causes Dysregulation of Gene Networks

We also observed a dysregulation of gene networks in response to noise, identifying potential marker genes associated with noise within the vasculature. This was accompanied by impaired endothelial and vascular signaling. Among the 4 most upregulated genes compared with controls were ZBTB44 (zinc finger and BTB domain containing 44), SETD4 (SET domain containing 4), YPEL2 (Yippee like 2), and IHH (Indian hedgehog signaling molecule). Conversely, the expression of SACS (sacsin molecular chaperone), NBEAL1 (neurobeachin like 1), PTPN4 (protein tyrosine phosphatase nonreceptor type 4), and NR4A3 (nuclear receptor subfamily 4 group A member 3) transcripts in aortic tissue was

significantly reduced by noise. These genes are linked to TGF-beta (transforming growth factor-beta) signaling, autophagy, growth, matrix metalloprotease regulation, and fibrosis.¹⁶ Cellular pathway analysis unveiled alterations in NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and adrenergic signaling, focal adhesion, cell cycle control, apoptosis, and kinase-mediated growth and proliferation signaling, with Foxo transcription factors playing a central role. Noise also adversely influenced the circadian rhythm, insulin, and calcineurin signaling pathways.^{16,87}

The Central Role of Nighttime Noise for Impaired Circadian Rhythm

As opposed to the awake phase, exposure of mice to aircraft noise during sleep had a substantially more detrimental impact on the cardiovascular system, leading to endothelial dysfunction, increased blood pressure responses, higher levels of neurohormones, the vasoconstrictor endothelin-1, and oxidative stress in the plasma, the vasculature, and the brain (Figure 4).⁸⁷ Additionally, it resulted in dysregulation of central and peripheral *Foxo3* (forkhead box protein 3)/circadian clock signaling, shown using RNA sequencing. A crucial finding was that aircraft noise-induced vascular and cerebral damage was strongly mitigated by knockout of the *Nox2* gene, underscoring the vital role of inflammatory cells in mediating noise-induced cardiovascular and cerebral side effects.⁸⁷ Surprisingly, within 4 days of continuous noise exposure, noise also triggered a significant downregulation and uncoupling of nNOS (neuronal nitric oxide synthase), creating a neuroinflammatory phenotype, as indicated by markers of inflammation and astrocyte activation.⁸⁷ This enhanced formation of cerebral ROS could partially explain the observed impairments in cognitive development, especially in learning and memory, in children exposed to aircraft noise.¹¹³

Novel Aspects of Noise Pathomechanisms

No Tolerance to Cardiovascular Side Effects of Noise

To test whether chronic exposure to aircraft noise results in noise habituation, we exposed animals to noise for up to 28 days, revealing persistent endothelial dysfunction and elevated blood pressure.¹¹⁴ Additionally, there was a time-dependent increase in the formation of ROS, as observed through dihydroethidium staining and HPLC-based superoxide measurements in the aorta, heart, and brain. The oxidative burst in whole blood peaked after 4 to 7 days of noise exposure. Increased superoxide in the brain coincided with the downregulation of *Nos3* and the transcription factor *Foxo3* genes. Conversely, VCAM-1 (vascular cell adhesion protein 1) mRNA, a marker of inflammation, was upregulated in all noise exposure

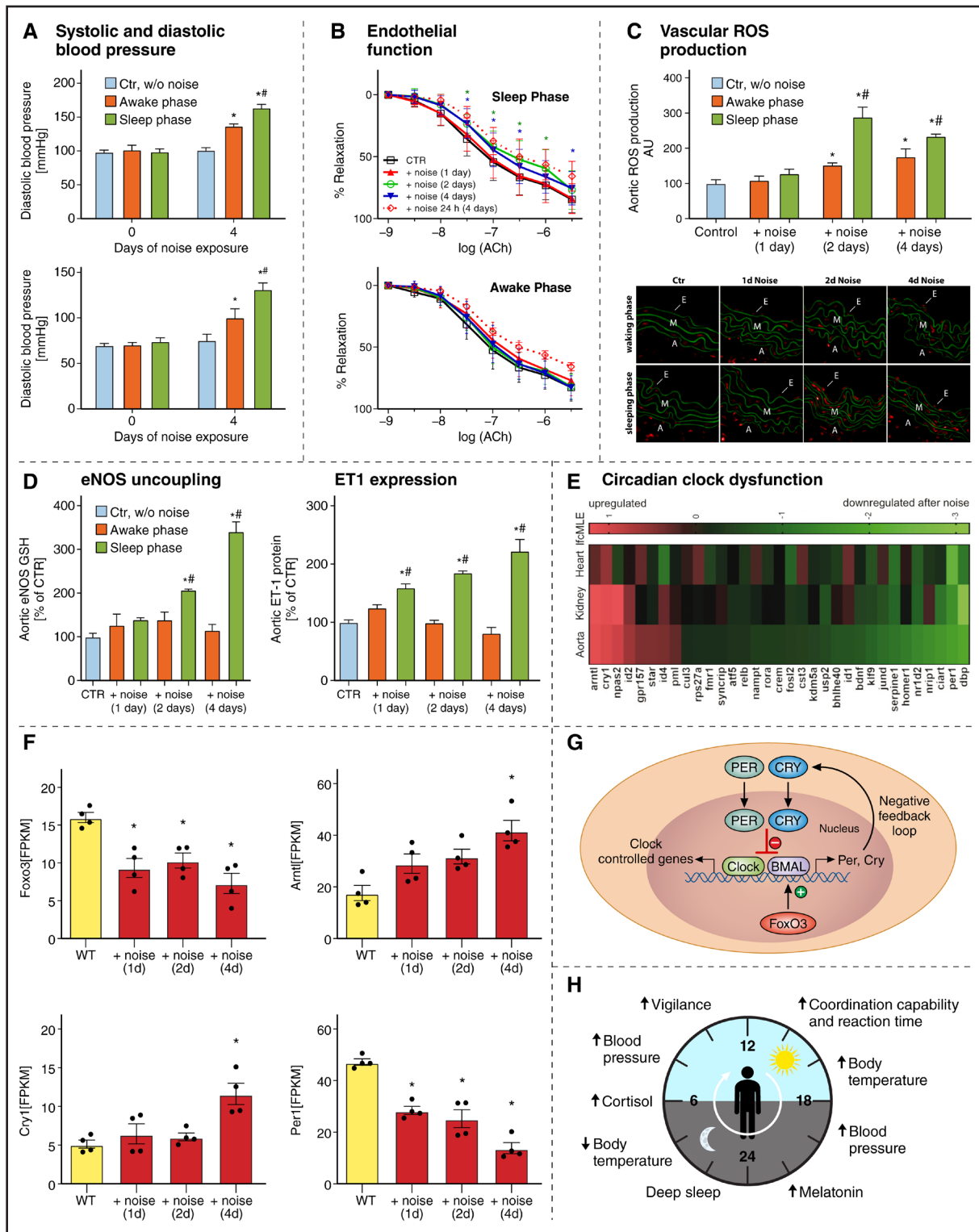


Figure 4. Effects of sleep and awake phase aircraft noise (mean sound pressure level 72 dB[A] for 12 h per day for 1, 2, and 4 days) on the murine vasculature.

Sleep phase noise showed a more pronounced increase in systolic and diastolic blood pressures (**A**) and caused significant endothelial dysfunction (diminished response to acetylcholine [ACh]; **B**). For comparison, the impaired endothelium-dependent relaxation in response to 24-h noise exposure is shown in a dotted line. Sleep phase noise induced more vascular oxidative stress (red fluorescence staining by oxidized hydroethidium in aortic cryo sections, reactive oxygen species (ROS); **C**) and eNOS (endothelial nitric oxide synthase) uncoupling by immunostaining against S-glutathionylated (=uncoupled) enzyme (eNOS-GSH) and endothelin-1 (ET-1) protein expression by immunohistochemistry (**D**). **E**, Sleep phase noise also caused substantial dysregulation of expression of circadian clock genes in the aorta and kidney as revealed by Illumina RNA sequencing. Aortic gene expression of the transcription factor Foxo3 (forkhead box protein 3, (Continued)

groups. Endothelial dysfunction and inflammation persisted throughout 28 days of aircraft noise exposure. The formation of ROS increased gradually with ongoing exposure, indicating that mice did not habituate to chronic noise stress at moderate levels.¹¹⁴

Noise Preconditioning and MI

A significant clinical question concerns whether the side effects of noise are aggravated in susceptible patients, for example, patients with acute coronary syndromes. We addressed this by exposing mice to an average sound pressure level of 72 dB and a peak level of 85 dB for up to 4 days, activating proinflammatory aortic gene expression related to myeloid cell adhesion and diapedesis pathways.¹¹⁵ Noise exposure promoted adhesion and infiltration of inflammatory myeloid cells in vascular and cardiac tissues, accompanied by an increased percentage of leukocytes exhibiting a proinflammatory phenotype, characterized by ROS and upregulation of Nox2 and phosphorylation of NF- κ B in peripheral blood.¹¹⁵ This proinflammatory phenotypic switch of circulating immune cells and cardiac tissue suggests a preconditioning of the heart for future ischemic heart damage. Subsequently, ligation of the left anterior descending artery was performed to induce MI. This resulted in a decline in cardiac function, substantial infiltration of CD11b⁺ (cluster of differentiation 11b) myeloid cells and Ly6C^{high} monocytes into the cardiac tissue, and the induction of IL-6, IL-1 β , CCL-2, and Nox2. These effects were intensified when noise exposure had occurred before MI (Figure 5). There was also an increase in mitochondrial O₂⁻ production due to a reduction in the oxygen consumption rate. The MI induced more pronounced endothelial dysfunction and increased vascular ROS levels in animals preconditioned with noise.¹¹⁵ These observations are in accordance with the previous finding that noise-mediated vascular damage was efficiently prevented when proinflammatory subsets of myelomonocytic cells were ablated using a genetic mouse model of specific depletion of LysM (lysine motif)-positive cells based on LysM-specific overexpression of a diphtheria toxin receptor.¹¹⁶

In a translational approach, we prospectively investigated participants in the Gutenberg Health Study Cohort. Among cases with an incident MI during follow-up, we observed that individuals with a history of noise exposure and annoyance exhibited elevated CRP levels at baseline and a more substantial decline in left ventricular ejection fraction after the MI.¹¹⁵ Accordingly, in a prospective study, people with verified acute coronary

syndromes were found particularly susceptible to the effects of aircraft noise.¹¹⁷ The HR for recurrence of cardiovascular events was 1.24 (95% CI, 0.97–1.58) per 10-dB increase in L_{den} aircraft noise. A combined analysis of recurrence (defined as MI, stroke, bypass surgery, or percutaneous coronary intervention with stent implantation) and all-cause mortality yielded an HR of 1.31 (95% CI, 1.03–1.66). Similar HRs were found for L_{day} and L_{night} aircraft noise exposure. HRs for road traffic and railway noise were above unity but insignificant. In summary, studies based on both humans and animals indicate that patients with CVD are highly susceptible to noise.

How Long Does the Cardiovascular System Need to Recover After Noise Stress?

Following a continuous exposure period lasting 4 days, the cessation of noise for either 1, 2, or 4 days proved sufficient to normalize noise-induced endothelial dysfunction in the aorta completely (in mice).¹¹⁸ This improvement was assessed through the measurement of acetylcholine-dependent relaxation. Furthermore, vascular oxidative stress and increased blood pressure exhibited partial correction, and markers of inflammation, including VCAM-1, IL-6, and leukocyte oxidative burst, returned to normal levels within 4 days of noise cessation. In contrast, the endothelial dysfunction, oxidative stress, and inflammation observed in the cerebral microvessels of noise-exposed mice showed no improvement. These results emphasize that the recovery process from noise-induced damage is more intricate than anticipated. While large conductance vessel function could be completely restored, persistent endothelial dysfunction in the microcirculation was evident. These findings suggest that, in general, more extended periods of noise cessation are required to reverse noise-induced vascular dysfunction, including the resistance vessels.¹¹⁸

Noise-Induced Side Effects Can Be Modified via Nonpharmacological and Pharmacological Activation of the α 1 AMP-Activated Protein Kinase

Nondrug approaches, including maintaining a routine of physical activity, adopting a well-balanced, healthy diet, and managing weight, have proven effective in preventing and treating CVDs and diabetes.¹¹⁹ Also, regular exercise is considered a means to mitigate the impact of air pollution-induced CVD and mortality.¹²⁰

We recently explored the potential protective effects of α 1AMPK (α 1 AMP-activated protein kinase)

Figure 4 Continued. which regulates BMAL1) and Per1 (period-1) were downregulated. **F**, In contrast, brain and muscle aryl hydrocarbon receptor nuclear translocator (Arnt)-like (Bmal) 1 and cryptochrome-1 (Cry1) were upregulated. **G**, The clock core components consist of the positive regulators *CLOCK* and *BMAL* that directly control circadian gene expression and the negative regulators *PER* and *CRY*. **H**, The circadian clock regulates several essential biological functions. **A** through **F** were adapted from Kroller-Schon et al⁸⁷ with permission. Copyright ©2018, Oxford University Press. **G** and **H** were adapted from Münzel et al⁸⁶ with permission. Copyright ©2020, Annual Reviews. Illustration credit: Sceaney Studios.

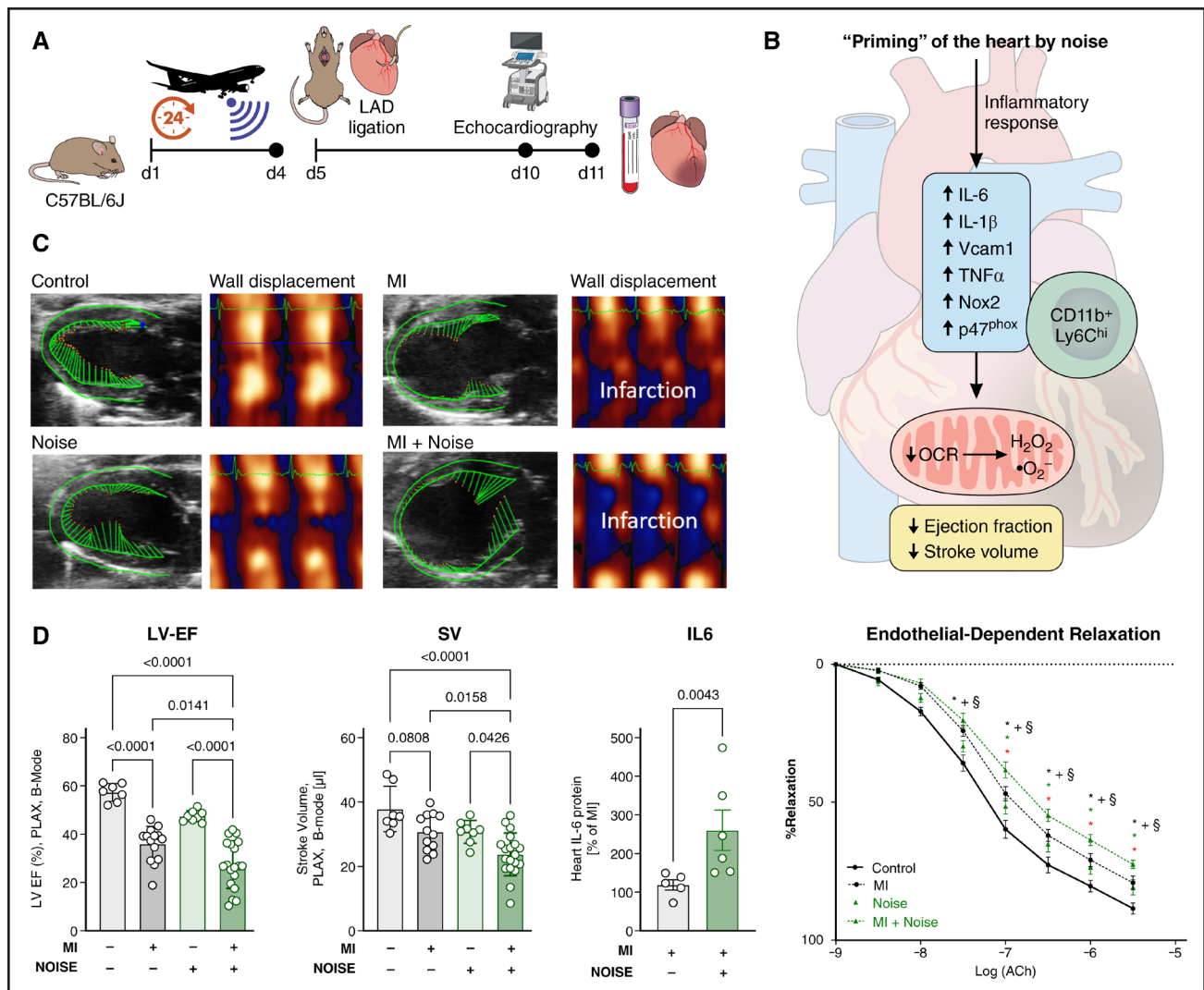


Figure 5. Noise exposure worsens cardiac and endothelial function after acute myocardial infarction (MI).

A, Experimental study scheme with noise exposure before experimental MI by left anterior descending artery (LAD) ligation, followed by delayed echocardiography. **B**, Noise exposure induces an inflammatory and pro-oxidative phenotype of the heart promoting exacerbation of impaired cardiac function and decreased oxygen consumption rate (OCR) leading to increased mitochondrial production of reactive oxygen species after MI (**C**). Representative B-mode images in parasternal long axis (PLAX) and heat map of wall displacement. **D**, High-frequency small-animal echocardiography 6 d after permanent LAD-ligation or sham operation with or without noise exposure revealed additively decreased left ventricular ejection fraction (LVEF in %) and stroke volume (SV in μ l). Increased cardiac IL (interleukin)-6 levels support the noise-mediated priming of the heart. **E**, Noise-induced additive endothelial dysfunction (impaired response to acetylcholine [ACh]) of the aorta after MI. CD11b indicates cluster of differentiation 11b; Ly6C, lymphocyte antigen 6 family member C1; Nox2, nicotinamide adenine dinucleotide phosphate oxidase subunit 2; p47^{phox}, nicotinamide adenine dinucleotide phosphate oxidase subunit; TNF α , tumor necrosis factor alpha; and VCAM-1, vascular cell adhesion protein 1. Adapted from Molitor et al¹¹⁵ with permission. Copyright ©2023, European Society of Cardiology. Illustration credit: Sceyence Studios.

activation through exercise, intermittent fasting, and pharmacological activation by 5-aminoimidazole-4-carboxamide riboside in a murine model of vascular dysfunction-induced aircraft noise.¹²¹ Mice were subjected to aircraft noise exposure, significantly impairing endothelial function in the aorta, mesenteric arteries, and retinal arterioles. This dysfunction was accompanied by an elevation in vascular oxidative stress and the formation of asymmetrical dimethylarginine. Importantly, activation of α 1AMPK using all 3 approaches

effectively prevented the onset of endothelial dysfunction and vascular oxidative stress, a conclusion supported by RNA sequencing data (Figure 6). Notably, the absence of endothelium-specific α 1AMPK worsened noise-induced vascular damage and nullified the positive effects of exercise or intermittent fasting.¹²¹ These outcomes substantiate that activating endothelium-specific α 1AMPK through pharmaceutical stimulation, exercise, and intermittent fasting effectively mitigates noise-induced cardiovascular damage.

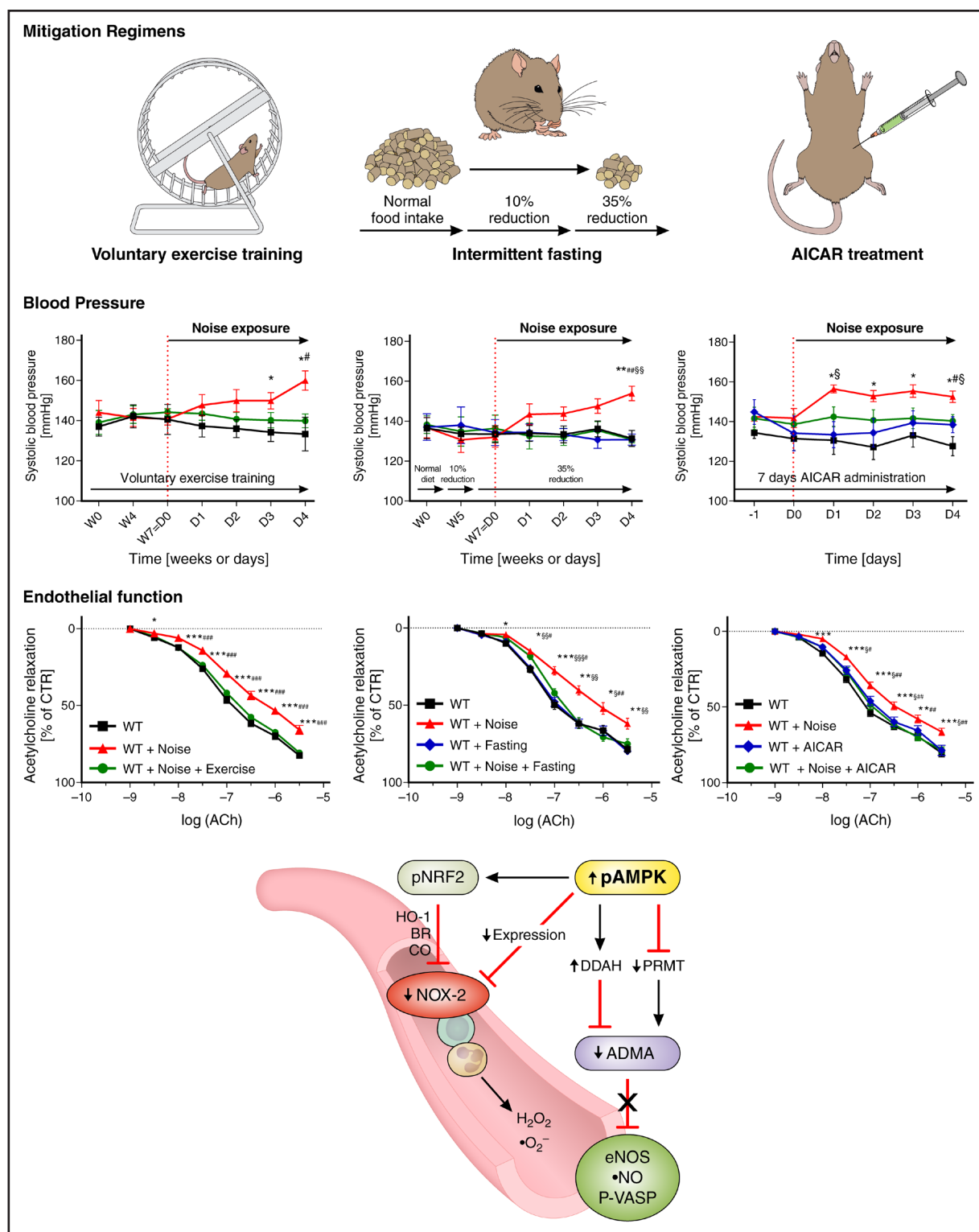


Figure 6. Exercise, caloric restriction, and 5-aminoimidazole-4-carboxamide riboside (AICAR) treatment prevented noise-induced elevation of blood pressure and endothelial dysfunction.

The interventions all restored noise exposure-induced blood pressure elevation to the level of unexposed control. Also, noise-triggered endothelial dysfunction (impaired response to acetylcholine [ACh]) in the aorta was prevented by the 3 interventions. The proposed protective mechanism of the 3 mitigation regimens is the activation of $\alpha 1$ AMPK ($\alpha 1$ AMP-activated protein kinase) leading downstream to an increase of the dimethylarginine dimethylaminohydrolase (DDAH), the degrading enzyme of asymmetrical dimethylarginine (ADMA), and a decrease of protein arginine methyltransferase 1 (PRMT1), an enzymatic source of ADMA. This will lead to lower levels of ADMA, the most potent endogenous eNOS (endothelial nitric oxide synthase) inhibitor, and, thereby, to more efficient nitric oxide signaling, all of which prevents noise-induced endothelial dysfunction. Activation of $\alpha 1$ AMPK also prevents noise-triggered NOX-2 (nicotinamide adenine dinucleotide (Continued)

THE INTERPLAY BETWEEN NOISE POLLUTION AND THE NEUROENDOCRINE AXIS

When noise exposure occurs during sleep, sleep fragmentation and abbreviated sleep periods may lead to significant life stress. This situation is known to initiate cerebral oxidative stress, primarily driven by heightened angiotensin-II signaling and activation of NOX-2; both have the potential to incite inflammation in the brain's microvasculature.¹²² In support, noise-exposed animals exhibit elevated circulating levels of the neurohormone angiotensin-II (Figure 7).^{16,123}

In animals, activation of the sympathetic nervous system due to oxidative stress induced by NADPH oxidase is the connecting link between renin-angiotensin-aldosterone system-mediated NOX-2 activation and subsequent release of catecholamines.^{124,125} Conversely, catecholamines can incite oxidative stress in rats by modulating monoamine oxidase activity or activating astrocytes, microglia, and NOX-2.¹²⁶ Consistent with the concept of a renin-angiotensin-aldosterone system-ROS-sympathetic nervous system axis, administering NADPH oxidase inhibitors reduces blood pressure and levels of angiotensin-II and noradrenaline in hypertensive mice.¹²⁷ Furthermore, oxidative stress in the heart and vasculature is mitigated through the blockade of the angiotensin-II receptor type 1 receptor and inhibition of the ACE.^{128,129}

Aircraft noise triggers an increase in the expression of endothelin-1 in the aorta of mice secondary to increased oxidative stress.¹³⁰ Endothelin-1 is a potent vasoconstrictor and activates NOX-2, which is partially dependent on the renin-angiotensin-aldosterone system.^{16,87,131}

These findings put forth a comprehensive molecular and pathophysiological framework that could account for the endothelial dysfunction and hypertension observed in animal models of noise exposure. This framework attributes a central role to NOX-2-induced oxidative stress and inflammation and the disruption of circadian rhythm caused by sleep fragmentation and deprivation. Most notably, these animal-based data strongly support the pivotal role of stress-response pathways in inducing adverse cardiovascular and cerebral effects in humans exposed to noise. They also provide detailed molecular mechanisms that outline the sequence of events within the brain and along the stress-response axis (Figure 7).

Importantly, a recent study showed that the amygdala, a part of the limbic system primarily involved in stress perception and emotional regulation, acts as a cerebral link between noise stimuli, vascular inflammation, and adverse cardiovascular events.¹³² Based on clinical

imaging to measure amygdala metabolic activity and arterial inflammation in 498 adults without preexisting CVD or active cancer, the study found that road and aircraft noise exposure was associated with increased amygdala activity and vascular inflammation. Furthermore, a mediation analysis indicated that higher noise exposure was associated with major adverse cardiovascular events through a sequence involving heightened amygdala activity and arterial inflammation. This association remained robust, with an HR of 1.34 (95% CI [CI]: 1.15–1.57) per 5-dB(A) increase in noise levels, even after multivariable adjustments.¹³² Accordingly, a subsequent report demonstrated that among individuals chronically exposed to socioeconomic or environmental stressors, a higher degree of resilience, defined as lower amygdala activity despite stress exposure, was associated with a >50% reduction in major adverse cardiovascular event risk, potentially via reduced arterial inflammation, suggesting that enhancing resilience may decrease the CVD burden in response to these stressors.¹³³ Importantly, the link between the brain and heart/vessels can also work in the other direction; CVD can also affect mental health.¹³⁴ However, noise can also change our lifestyle and by this pathway impact cardiovascular health.

COEXPOSURE TO NOISE AND AIR POLLUTION

Comparative analyses of the disease burden reveal that air pollution is the foremost environmental contributor to disability-adjusted life years lost, whereas environmental noise ranks second.¹³⁵ Air and noise pollution often share common sources, including aircraft, trains, and road vehicles, resulting in simultaneous exposure to noise and air pollution. Research suggests that the EU faces substantial noise and air pollution costs, encompassing excess deaths and diseases, reaching nearly 1 trillion EUR. In comparison, the cost related to alcohol consumption in the EU is estimated at 50 to 120 billion EUR and smoking at 544 billion EUR.¹³⁶ Several studies on transportation noise have incorporated mutual adjustment for air pollution. A review from 2023 concluded that air pollution did not seem to confound the association between noise and cardiovascular health, strongly indicating that transportation noise and air pollution independently increase the risk of CVD.¹³⁷ The review also concluded that more studies on potential interactions between these 2 exposures were needed.

To investigate this further, we used an exposure system with an aerosol generator and loudspeakers,

Figure 6 Continued. phosphate oxidase subunit 2) expression/activation and oxidative stress, in part by cross-activation of NRF2 (nuclear factor erythroid 2-related factor 2) via specific phosphorylation and subsequent HO-1 (heme oxygenase-1) induction followed by carbon monoxide (CO) and bilirubin (BR) production. Adapted from Kvandova et al¹²¹ with permission. Copyright ©2023, European Society of Cardiology. Illustration credit: Sceyence Studios.

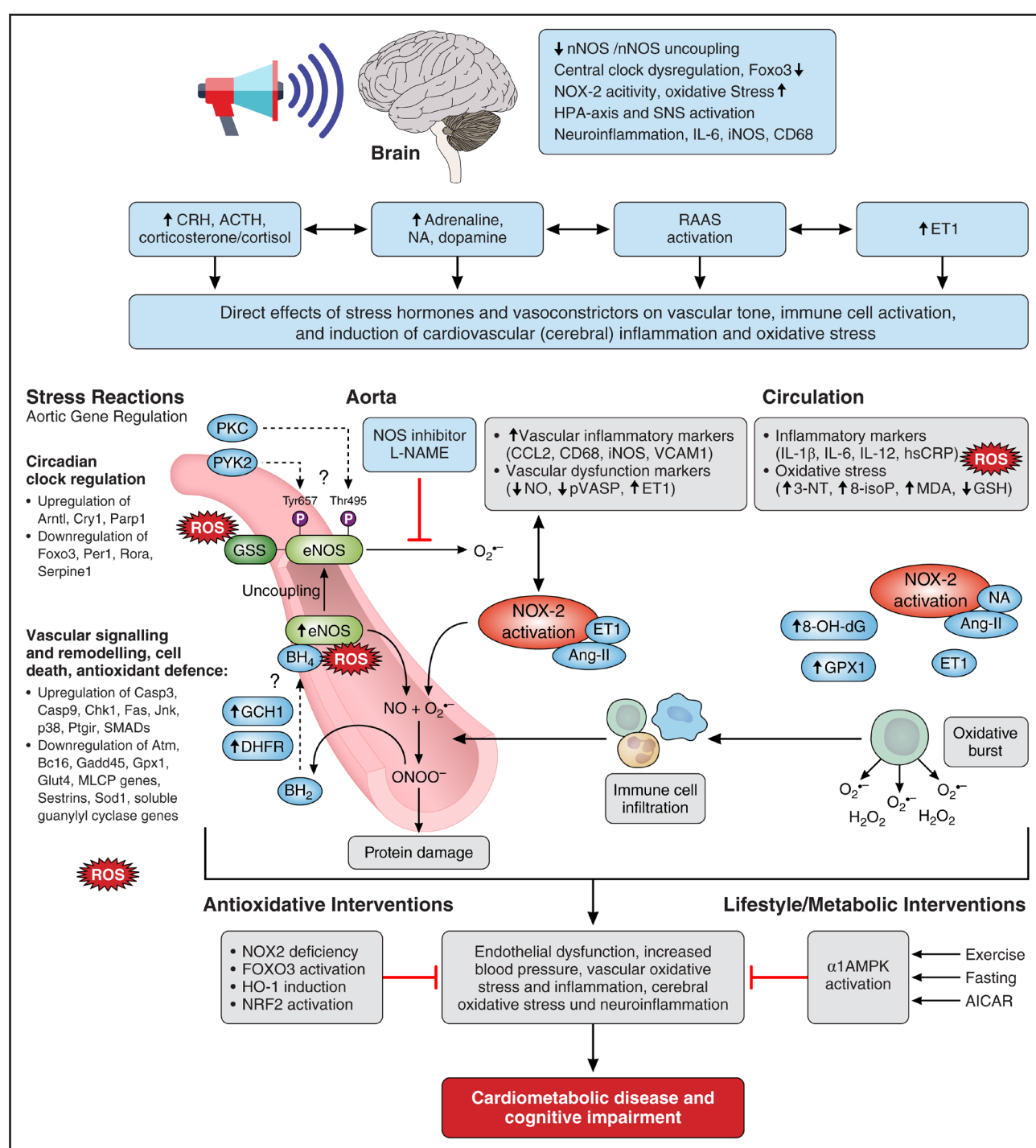


Figure 7. Proposed mechanistic pathway between transportation noise and cerebral and cardiovascular disease.

3-NT indicates 3-nitrotyrosine; 8-isoP: 8-isoprostane; 8-OH-dG, 8-oxo-2'-deoxyguanine; ACTH: adrenocorticotrophic hormone; AICAR, 5-aminoimidazole-4-carboxamide riboside; Ang-II, angiotensin-II; ARNTL, aryl hydrocarbon receptor nuclear translocator like; BH₂, dihydrobiopterin; BH₄, tetrahydrobiopterin; CASP3/9, caspase3/9; CCL2, chemokine (C-C motif) ligand 2; CD68, cluster of differentiation 68 (macrosialin); CHK1, checkpoint kinase 1; CRH, corticotropin-releasing hormone; CRY1, cryptochrome-1; DHFR, dihydrofolate reductase; eNOS, endothelial nitric oxide synthase; ET1, endothelin-1; Foxo3, forkhead box protein 3; GADD45, growth arrest and DNA damage 45; GCH1, GTP cyclohydrolase 1; GFAP, glial fibrillary acid protein; GLUT4, glucose transporter type 4; GPX1, glutathione peroxidase 1; GSH, glutathione; GSS-, S-glutathionylation; H₂O₂, hydrogen peroxide; HO-1, heme oxygenase-1; HPA, hypothalamic-pituitary-adrenal; hscsod 1 IL, interleukin; iNOS, inducible nitric oxide synthase; L-NAME, N^G-nitro-L-arginine methylester; MDA, malondialdehyde; MLCP, myosin light chain phosphatase; NA, noradrenaline; nNOS, neuronal nitric oxide synthase; NOX2, nicotine adenine dinucleotide phosphate oxidase isoform 2 (phagocytic nicotinamide adenine dinucleotide phosphate oxidase); NRF2, nuclear factor erythroid 2-related factor 2; O₂⁻, superoxide; ONOO⁻, peroxynitrite; PARP1, poly (ADP-ribose) polymerase 1; Per1, period-1; PKC, protein kinase C; PTGIR, prostaglandin I₂ receptor; pVASP, phosphorylated vasodilator-stimulated phosphoprotein; PYK2, protein tyrosine kinase 2; RAAS, renin-angiotensin-aldosterone system; RORα, RAR-related orphan (Continued)

subjecting mice to acute exposure for 3 days to ambient particulate matter and aircraft noise. Both stressors led separately to a significant degree of endothelial dysfunction in arterial conductance and cerebral resistance vessels, increased blood pressure, oxidative stress, and inflammation.¹³⁸ An additional impairment of endothelial function was observed in isolated aortic rings and was even more pronounced in cerebral and retinal arterioles. The increase in oxidative stress and inflammation markers, coupled with RNA sequencing data, pointed to noise primarily affecting the brain and particulate matter affecting the lungs. The combined impact of both stressors exhibited additive adverse effects on the cardiovascular system, likely driven by particulate matter-induced systemic inflammation and noise-induced stress hormone signaling.¹³⁸ These studies also revealed an additive upregulation of ACE-2 in the lungs.

These data underscore the need for further mechanistic studies to elucidate the propagation of primary target tissue damage from the lung and brain to remote organs, such as the aorta and heart, resulting from combined noise and particulate matter exposure.¹³⁸

NOISE MITIGATION MANEUVERS

Local authorities can use various strategies to mitigate the noise from roads, railways, and aircraft. For road traffic, it is important to note that at speeds exceeding 30 to 35 km/h for cars and 55 to 65 km/h for heavy vehicles, emitted noise arises primarily from the contact between tires and the road surface. Consequently, the transition from combustion engine cars to electric vehicles will only result in minor reductions in road traffic noise, ≈ 1 dB(A). Several established strategies can be used to reduce road traffic noise. These include noise barriers erected along busy roads in densely populated areas, which will significantly reduce noise levels (up to 10 dB(A)), and noise-reducing asphalt, which can lead to noise reductions ranging from 3 to 6 dB(A). Speed limit adjustments lead to ≈ 1 -dB(A) reduction per 10-km/h reduction in the speed limit. Developing and promoting low-noise tires can potentially reduce noise levels at a national scale by ≈ 2 to 3 dB(A). Also, investments in urban infrastructure, promoting the use of bikes, ride shares, and public transport, will result in an urban noise reduction. Because these individual abatement strategies often result in relatively small noise reductions, combining these approaches may be needed in densely populated areas.

For aircraft noise, strategies to reduce population exposure include the implementation of optimized air

traffic routes via GPS guiding to minimize overlap with densely populated areas. Implementing night flight bans, during which takeoffs and landings are not allowed, can significantly reduce nighttime aircraft noise. A continuous descend approach using steeper descents with lower and less variable throttle settings can help to minimize noise during aircraft approaches and landings.

In the context of railway noise, preferred strategies for reducing noise include rail grinding, meaning regular maintenance, and grinding of railway tracks to reduce wear and noise. Using brake upgrades means replacing cast-iron block brakes with composite materials that generate less noise during train operations. Night-time operation bans on railway operations near residential zones are a powerful tool to reduce nighttime noise disturbances.

CONCLUSIONS, POLITICAL, AND SOCIETAL CONSEQUENCES

The comprehensive compilation of preclinical, clinical, and epidemiological evidence strongly reinforces the notion that transportation noise serves as a significant environmental factor contributing to the development of various cardiovascular and cerebrovascular conditions, including chronic coronary artery disease, acute coronary syndrome, arterial hypertension, stroke, and heart failure.

The findings from recent translational studies involving animals and humans support the idea that noise is linked to disruptions in redox balance and vascular function and disturbances in autonomic and metabolic processes. These noise-related effects not only exacerbate the adverse health consequences of traditional cardiovascular risk factors, such as arterial hypertension and diabetes, but also accelerate atherosclerotic processes and increase the overall risk of CVD. Nevertheless, it is essential to acknowledge that while preclinical animal studies provide valuable insights, they may only sometimes be entirely applicable to human noise-related health effects due to species-specific differences in hearing range and noise perception. As a result, these findings should be interpreted cautiously. However, a major result of animal research is that the sound pressure level itself maybe not the key determinant of noise-inflicted cardiovascular damage, but frequency or noise pattern may be more important. Accordingly, it is highly warranted to look at the health effects of different noise sources.

Noise and air pollution are correlated as they are emitted from common sources, most importantly aircraft, trains, and road vehicles. The estimated costs of coexposure to

Figure 7 Continued. receptor alpha; ROS, reactive oxygen species; RP, high-sensitivity C-reactive protein; SERPINE1, serpin family E member 1; SMAD, suppressor of mothers against decapentaplegic; SNS, sympathetic nervous system; SOD1, superoxide dismutase 1; VCAM-1, vascular cell adhesion protein 1; and $\alpha 1$ AMPK, alpha1 AMP-activated protein kinase. Adapted from Munzel et al⁸ with permission. Copyright ©2021, Springer Nature Limited. Illustration credit: Sceyence Studios.

noise and air pollution greatly surpass those associated with alcohol and smoking.¹³⁶ Consequently, numerous research gaps warrant attention, including the assessment of the magnitude and time course of responses to coexposure to noise and air pollution, the exploration of the synergistic effects of both exposures on surrogate measures such as blood pressure and diabetes, and the determination of the duration of effects and their potential for reversal. There is also a need to investigate the impact of cardiovascular therapies, such as statins, ACE inhibitors, angiotensin-II receptor blockers, and AMP-kinase activators, on noise-induced and air pollution-induced health effects and their implications for future cardiovascular risk by studying the influence of noise on circadian rhythms and understanding the combined effects of noise in conjunction with lifestyle factors such as diet, stress, and exercise.

Regarding political consequences, the cardiovascular community is responsible for raising awareness of the impact of environmental pollutants. This goes beyond promoting healthy lifestyles and diets; it also involves taking steps to minimize the effects of noise pollution on cardiovascular health. However, recommendations to reduce noise pollution were absent from the European Society of Cardiology (ESC)¹¹⁹ and the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for prevention.¹³⁹

Considering the impact of noise on the cardiovascular system, does it still make sense to ask our patients only about traditional cardiovascular risk factors to assess the overall cardiovascular risk? We do not think so. Rather we must assess the so-called exposome or variety of exposures an individual encounters at different levels throughout life and how these exposures impact biology and health.¹⁴⁰ It comprises external and internal factors, including chemical (ie, air pollution), physical (ie, noise exposure), biological (ie, virus infections), and social factors (ie, mental stress) that may influence human health. The exposome will help to predict the risk for future CVD more precisely.

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Disclosures

Dr Münzel is a PI and Drs Molitor, Kuntic, Hahad, and Daiber are (young) scientists of the German Centre for Cardiovascular Research (DZHK), Partner Site Rhine-Main.

Supplemental Material

Figure S1

Tables S1–S3

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