Title: Transportation Noise Pollution and Cardiovascular Health

Authors:
Thomas Münzel (University Medical Center Mainz)
Omar Hahad (University Medical Center Mainz)
Michael Molitor (University Medical Center Mainz, Johannes Gutenberg-University, Center for Cardiology)
Marin Kuntic (University Medical Center Mainz, Germany)
Martin Röösli (Swiss Tropical and Public Health Institute, Department Epidemiology and Public Health, University of Basel, Switzerland)
Nicole Engelmann (Swiss Tropical and Public Health Institute, Department Epidemiology and Public Health, University of Basel, Switzerland)
Mathias Basner (University of Pennsylvania)
Andreas Daiber (Universitätsmedizin Mainz)
Mette Sørensen (Danish Cancer Society Research Center)

Transportation Noise Pollution and Cardiovascular Health

Short Title: Noise and Cardiovascular Health

Thomas Münzel MD[1,2]
Omar Hahad PhD[1,2]
Michael Molitor MD[1,2]
Marin Kuntic PhD[1]
Martin Röösli PhD[3]
Nicole Engelmann PhD[3,]
Mathias Basner PhD[4]
Andreas Daiber PhD[1,2*]
Mette Sørensen PhD[5,6*]

[1]: University Medical Center Mainz, Department of Cardiology, Germany
[2]: German Centre for Cardiovascular Research (DZHK); Partner site: Rhine-Main, Germany
[3]: Swiss Tropical and Public Health Institute, Department Epidemiology and Public Health, University of Basel, Switzerland
[5]: Unit for Experimental Psychiatry, Division of Sleep and Chronobiology, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, USA
[6]: Danish Cancer Institute, Danish Cancer Society, Denmark
[7]: Department of Natural Science and Environment, Roskilde University, Roskilde, Denmark

University Medical Center
Johannes Gutenberg University Mainz
Langenbeckstrasse 1
55131 Mainz
Tel.: +496131177250
Fax:+49 6131 17 6615
Email: tmuenzel@uni-mainz.de

*Both authors contributed equally and should be considered as joint senior authors
Word count: 14,092 without title page and abstract

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, non-auditory 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, 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. Potential effects of noise on alterations of gene networks, epigenetic pathways, circadian rhythm, signal transduction along the neuronal-cardiovascular-axis, oxidative stress, inflammation, and metabolism will be elaborately explained. Current and future noise mitigation strategies will be described. Lastly, we will conduct an overall evaluation of the status of the current evidence of noise as a significant cardiovascular risk factor.

Introduction

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 like acute myocardial infarction (MI), heart failure, arrhythmia, hypertension, and stroke (for review see[1]). Recent studies have identified particulate matter with a diameter of <2.5µm (PM2.5) as a leading air pollutant contributing to approximately 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.[3,4] Noise is defined as "unwanted and/or harmful sound " and includes transportation, occupational, leisure, residential, and industrial noise (Figure 1).[5]

In their 2020 report, the European Environment Agency (EEA) highlighted that many people remain exposed to high road traffic noise levels.[6] EEA estimated that at least 20% of the population in the European Union (EU) resides in urban areas where traffic noise adversely affects health, though this number is considered strongly underestimated.[6] The population's exposure to environmental noise is projected to increase due to urban expansion and growing demand for mobility.[7] 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, Supplement Table 1) by 7.8% and railway noise by 11.8% within urban areas and 16.4% and 8.7%, respectively, outside urban areas by 2030.[7] In contrast, the exposure to aircraft noise will remain unchanged inside and outside metropolitan area.[7]

In this review, our primary focus is to explore the indirect, non-auditory 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 encompass alterations in gene networks, epigenetic pathways, circadian rhythms, signal transmission within the neuronal-cardiovascular connection, oxidative stress, inflammation, 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 regarding noise as a risk factor for cardiovascular health.

Noise and the Global Burden of Disease

The global health burden arising from noise is substantial. Road traffic noise above 55 dB(A) L_{den} affects 113 million Europeans, mainly in urban areas.[8] Furthermore, 22 million are exposed to railway noise and 4 million to aircraft noise above 55 dB(A). According to the World Health Organization (WHO), adverse health impacts are likely at this noise level.[9] Noise exposure at night is even more detrimental, and the WHO recommends that nocturnal noise from road traffic do not exceed 45 dB(A) (L_{night}).[9] Annually in 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.[7] Nevertheless, these statistics fail to capture the full extent of the health burden, as adverse effects are now observed at lower noise exposure levels than previously recognized, affecting a broader range of health outcomes.

How Noise Causes Cardiovascular Disease: The Noise Reaction Scheme

Wolfgang Babisch introduced the noise reaction model in which an indirect pathway plays a pivotal role in the development and progression of CVD.[10] 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 like acute and chronic coronary syndrome, heart failure, persistent hypertension, arrhythmias, and stroke (for review see[11]). Noise also disrupts sleep, daily activities, and communication, causing annoyance and reduced sleep quality and duration, potentially linked with increased risk of CVD[11] (Figure 1). The noise-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system triggers the release of stress hormones like cortisol and catecholamines. This, in turn, induces inflammation, leading to increased levels of IL-6, IL-1β, and proinflammatory monocytes, along with oxidative stress. Nighttime exposure to aircraft noise has even been linked to stress-induced cardiomyopathy, also known as Takotsubo Syndrome.[12] Stress responses can increase blood pressure, potentially impairing vascular function. This affects endothelial nitric oxide synthase (eNOS), 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).

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.[13] 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 significant adverse cardiovascular events (MACE) through a sequence involving heightened amygdala activity and arterial inflammation. This association remained robust, with a hazard ratio (HR) of 1.34 (95% confidence interval [CI]: 1.15–1.57) per 5 dB(A) increase in noise levels, even after multivariable adjustments.[13] Accordingly, a subsequent report demonstrated that among individuals chronically exposed to socioeconomic or environmental stressors, a higher degree of resilience was associated with a >50% reduction in MACE risk, potentially via reduced arterial inflammation, suggesting that enhancing resilience may decrease the CVD burden in response to these stressors.[14]

Epidemiological Evidence

Transportation Noise and Cardiovascular Disease and Death

Over the past years, there has been a growing body of evidence on the effects of environmental noise on cardiovascular health. The meta-analyses commissioned by the WHO that were published as part of the Environmental Noise Guidelines for the European Region from the World Health Organization (WHO ENG)[15] included studies published until 2015. Subsequent studies have been evaluated in a 2023 Umbrella+ review, including meta-analyses to obtain up-to-date exposure-response functions for CVD and mortality.[16] An Umbrella+ review summarizes results from the newest high-quality systematic reviews combined with original studies published after the corresponding review. Only original studies that applied reliable exposure assessment methods and accounted for the most relevant confounding factors were considered in the Umbrella+ review. For mortality and CVD, only cohort studies were included. In contrast, case-control and cross-sectional studies were included for

hypertension if they were large, population-based, and used established methods for outcome assessment.[16] Below is a summary of the Umbrella+ CVD results (Figure 2).

Cardiovascular mortality

The systematic literature search identified 61 potentially eligible cardiovascular and IHD mortality papers. Thereof, twelve prospective cohort studies on road, railway, and/or aircraft noise were eligible for meta-analysis (Supplementary Table 2). Supplement Figure 1 shows the results of the meta-analysis. Based on nine studies, the pooled effect estimate per 10 dB(A) of road traffic noise was 1.045 (95% CI: 1.017–1.073).[16] For railway and aircraft noise, only two studies were available for each exposure, suggesting either no or minimal effect of these two exposures on cardiovascular mortality (Supplement Figure 1).

Ischemic heart disease

A systematic review published as part of the WHO ENG,[15] 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 three cohort and four case-control studies.[17] 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 very low certainty of evidence.

Since then, many studies have been published investigating noise and IHD incidence. The most recent studies includes a pooled analysis of Danish and Swedish cohorts,[18] and a nationwide study with more than 2.5 million participants.[19] Both studies found road traffic noise to increase IHD incidence with 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.[18 19]

We found that in a meta-analysis combining the WHO ENG review[17] with three new cohort studies and the pooled Scandinavian cohort (Supplement Table 3), a 10 dB(A) increase in road traffic noise was associated an RR of 1.041 (95% CI: 1.023–1.059) for IHD incidence (Figure 2).[16] Corresponding RRs (95% CI) for aircraft and railway noise were 1.009 (0.992–1.026) and 0.996 (0.933–1.062), respectively.

Stroke

In the WHO ENG, only one cohort study on road traffic noise and incident stroke was available, finding an HR of 1.14 (95% CI: 1.03–1.25).[15] 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, nine studies on stroke were 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 a HR of 1.06 (95% CI: 1.03–1.08) per 10 dB(A) higher road traffic noise.[20]

In the Umbrella+ review we found that based on six cohort studies (Supplement Table 3), road traffic noise increased in the risk of incident stroke, with an RR per 10 dB(A) of 1.046 (95% CI: 1.013–1.081).[16] In contrast, aircraft and railway noise, both based on two studies, was not associated with stroke, with pooled RR (95% CI) of 0.995 (0.875–1.131) and 0.969 (0.955–0.984), respectively.

Heart failure

Neither the WHO ENG[15] nor any recent systematic review addressed heart failure in the context of noise exposure. However, six longitudinal studies addressed this association in recent years, all showing positive associations with an RR between 1.01 and 1.09 per 10 dB(A) increase in road traffic noise (Supplement Table 3). In an updated meta-analysis, we found road traffic noise to increase risk of heart failure, with a RR of 1.044 (95% CI: 1.017–1.071) per 10 dB(A) increase (Figure 2).[16] Two studies assessing railway noise indicated no or a positive association. For aircraft noise, a German study[21] showed a decrease in risk, whereas a Danish nationwide study presented a positive association with a RR of 1.06.[19] The pooled RR for railway and aircraft noise, derived from two studies each, were 1.011 (95% CI: 0.998–1.035) and 1.017 (95% CI: 0.934–1.107) 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. Further, only a few cohort studies exist. These studies include a Danish nationwide cohort study[22] 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 1–2% per 10 dB(A).

In an updated meta-analysis for road traffic noise based on three cohort studies, we found an RR of 1.006 (95% CI: 1.001–1.011) per 10 dB(A), whereas the pooled RR for aircraft noise, which was based on two studies, was 1.207 (95% CI: 0.699–2.084) per 10 dB(A).[16] Only one study provided an estimate for railway noise, which was 1.017 (95% CI: 1.008–1.027) per 10 dB(A).

Conclusions on cardiovascular incidence studies

Based on the Umbrella+ review, we conclude that solid 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). 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 two 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. It is currently uncertain at which level this lower effect threshold is. Also, the threshold likely varies between sources of noise. Different noise recommendation limits exist across the world. E.g., 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}).[9]

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 35–40 dB(A) (app. background level of noise) until 80–85 dB(A).[19,20,23-25] Many of these studies suggest that the effects of noise on morbidity and mortality start already from 35–40 dB(A), e.g., for stroke,[20,23] diabetes,[26] and cardiovascular mortality.[25,27] For IHD, studies have suggested a threshold between 50 and 55 dB(A).[19,24]

As illustrated in Table 1, 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 four potential lower effect thresholds 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.[28,29] We observed that the calculated numbers of IHD and CVD deaths due to road traffic noise were three to four 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

Arterial hypertension

A 2021 review assessed hypertension in relation to transportation noise and derived pooled estimates stratified by noise source and study type.[30] While the meta-analysis for road traffic noise showed no association for cohort and case-control studies, an increased odds of 9% per 10 dB(A) was seen in cross-sectional studies. No associations were observed for aircraft and railway noise. Since then, three studies have been published on aircraft noise and hypertension, of which two studies were based on populations from the USA, showing that comparing individuals exposed to above 45 dB(A) versus below 45 dB(A) resulted in increased risk of 0%[31] and 3%.[32] A French aircraft study found a significant risk increase of 36% per 10 dB(A).

In a meta-analysis pooling the risk estimates from cohort and cross-sectional studies, we found an RR of 1.04 (95% CI: 0.970–1.126) per 10 dB(A) road traffic noise and 1.031 (95% CI: 1.008–1.053) per 10 dB(A) aircraft noise.[16 30] 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 CVD patients,[33,34] and adverse effects of noise on these two 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.[26,35-41] A meta-analysis from 2023 found that a 10 dB(A) higher road traffic noise was

associated with an RR of 1.06 (95% CI: 1.03–1.09).[42] Interestingly, two studies have investigated 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.[26,43] These two 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 an essential mechanism. Furthermore, noise-induced endothelial dysfunction is suggested to contribute to the adverse metabolic effects noise.[44] In line, a recent study demonstrated that endothelial dysfunction can predict the onset and progression of type 2 diabetes.[45]

A handful of prospective cohort studies have investigated the effects of exposure to transportation noise on the risk of developing adiposity.[46-51] The measures of adiposity varied across the studies, with four studies investigating effects on weight gain/BMI,[46,47,49-51] two studies on waist circumference changes,[46,47] and two studies on the risk of obesity/overweight.[47,48] 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,[50,51] a pregnancy cohort,[49] and adult and elderly populations,[46-48] suggesting that exposure to road traffic noise may affect the risk of adiposity throughout life.

Mental health

Major depression and other psychological factors are acknowledged risk factors for CVD,[52] 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.[53] Since this meta-analysis, new longitudinal studies have supported that road traffic noise may increase the risk of depression and/or poorer mental health-being[54,55] and suicide.[56] One study furthermore suggested that the effects of road traffic noise on depression seemed to be partly mediated by annoyance towards noise,[54] supported by a prospective study showing that noise annoyance at baseline was associated with risk of depression and anxiety symptoms

five years later.[57] The observed linkage between transportation noise and depression needs confirmation in more high-quality prospective studies.

Unhealthy behaviour

A few studies have investigated whether road traffic noise is associated with unhealthy lifestyle habits,[58-60] which seems plausible as noise is believed to exert its harmful effects through two main pathways associated with lifestyle changes, namely stress and sleep disturbance. Effects of noise on leisure-time physical activity have been studied in two studies, investigating effects of estimated residential road traffic noise and self-reported transportation noise annoyance.[58,59] Both studies suggested that road traffic noise might have a negative impact on physical activity.[59] One study investigated the effects of road traffic noise on smoking and alcohol habits.[60] 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.

Sleep disturbance

Sleep societies recommend that adults obtain 7-9 hours of high-quality sleep to promote well-being and health.[61] Conversely, sleep that is disturbed or too short has been associated with increased mortality and several adverse health outcomes, first and foremost CVD.[62] 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.[63] Consequently, sleep will be shorter and lighter with less time spent in deep and REM sleep, which is crucial for sleep recovery. This is evidenced by increased daytime sleepiness and decreased performance after noisy nights.[64] Even when sleep stages are unaffected, noise can increase the number and intensity of autonomic arousals, negatively affecting metabolic and cardiovascular function.[63,65] In addition to the sound level, the sleep-disturbing properties depend on other noise characteristics like rise time and frequency content, but also the meaning of the sound to the recipient.[63]

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.[66] 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.[67,68] Noise also prevents blood pressure from dipping during the night,[69] with plausible long-term effects on CVD risk. Analysis of blood proteins showed that noise exposure induces changes indicative of a pro-thrombotic and pro-inflammatory state, providing a biological basis for the increased risks of CVD and other diseases like neurodegenerative disease, obesity, diabetes, and breast and colon cancer.[68] 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.[70] A recent retrospective case-crossover study at Zurich airport revealed an association between aircraft noise exposure levels in the two hours before an event and cardiovascular mortality.[71] 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 highly annoyed" (%HA) metric for clear communication.[72,73]

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 towards noise, socioeconomic status, public perception, perceived stress, and coping abilities.[74] In the WHO ENG, exposure-response relationships for road, railway, and aircraft noise estimated in meta-analyses, ranked aircraft noise as the most annoying.[75] Recent trends showed increased annoyance for aircraft and railway noise while remaining relatively stable for road traffic noise, necessitating further investigation into these variations.[76,77]

Noise annoyance can be an early indicator of more severe health risks due to its rapid onset compared to 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.[78]

Mechanistic Noise Studies in Humans and Animals

Cardiovascular effects of noise

The concept that non-auditory effects of noise contribute substantially to health consequences was suggested in a 1970 monography.[79] The monography described results showing that acute noise exposure had cardiovascular effects, e.g., a study establishing that noise exposure led to constricting peripheral blood vessels in individuals engaged in physical exercise.[80] 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.[81]

Among 1,005 German industrial workers, it was observed in 1968 that workers in very noisy industries exhibited more pronounced peripheral circulation problems, heart issues, and equilibrium disturbances than workers in less noisy industries.[82] 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 pressure.[83] Moreover, higher noise levels were significantly linked to elevated systolic and diastolic blood pressure and heart rate.[84] Later, a study found that nighttime transportation noise led to more pronounced increases in blood pressure compared to daytime exposure.[85] It was suggested that repeated nighttime autonomic arousals may disrupt the natural nocturnal decline in blood pressure.[69] Also, in workers exposed to occupational noise exceeding 80 dB(A) LAeq, a significant increase in systolic and diastolic blood pressure was observed along with elevated levels of glutathione peroxidase and DNA damage, compared to office workers exposed to between 40-50 dB(A) LAeq.[86]

Translational Studies of Transportation Noise on Endothelial Function in Humans

Through a series of field investigations (studies performed in the home of the subject), the adverse effects of aircraft and railway noise on vascular (endothelial) function, sleep quality, stress hormone release, and inflammation markers, both in healthy individuals and CVD patients were established.[67,87] Noise recorded in a bedroom near 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 (Leq) of 46.3 dB(A) and a peak level of 60 dB(A) for one 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).[87] Notably, the acute administration of vitamin C of 2g improved endothelial dysfunction 2h 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, i.e., previous exposure to Noise30 caused Noise60 to 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 markers 3-nitrotyrosine [3-NT] and 8-isoprostane serum levels in response to aircraft noise exposure (Figure 3).[70]

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.[67] Similar investigations were conducted in healthy subjects exposed to either 30 (Noise30) or 60 train events (Noise60) during the nighttime, with LAeq levels ranging from 33 to 54 dB(A) for one night (Figure 3).[88] This exposure decreased sleep quality and impaired the brachial artery's flow-mediated dilation (FMD). 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, pro-thrombotic, pro-inflammatory, and fibrotic pathways compared to controls.[88]

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 two nighttime aircraft noise scenarios, with comparable mean sound pressure levels: one with loud and infrequent noise events and one with less loud but more frequent noise events (Leq values of 37 dB(A) for control and 45 dB(A) for noise exposure for one night).[89] Both scenarios resulted in similar worsening of endothelial function (FMD). 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 three biomarkers (follistatin, glyoxalase I, and ACE-2) associated with regulating heart function, oxidative stress, inflammation, and fibrosis.[89]

Noise Causes Endothelial Dysfunction, 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 C-reactive protein (hsCRP) while decreasing natural killer cell populations and activity,[90,91] although these results are not consistently uniform across all studies.[65] Furthermore, alterations in the immune system have been linked to elevated circulating cortisol levels and heightened noise sensitivity.[90,91] Interestingly, a study based on the Swiss SAPALDIA cohort 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 (e.g. CRP), cellular development, and immune responses.[92] 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.[93] This finding is supported by a German cohort study, showing that long-term exposure to night-time road traffic noise was associated with subclinical atherosclerosis, especially in participants with early arterial calcification.[94,95] Thus, in summary, these findings offer pathophysiological and molecular evidence from

human studies, shedding light on 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).

Development of Animal Models to Study the Molecular Mechanisms of the Cardiovascular and Cerebral Side Effects of Transportation Noise

Noise causes vascular dysfunction, oxidative stress, inflammation, and dysregulation of gene networks

A novel animal model was established to study the molecular mechanisms underlying noise-induced cardiovascular and cerebral adverse effects. . This involved exposing mice to continuous aircraft noise (with a constant Leq of 72 dB(A) and peak levels of 85 dB(A) for 24 hours a day, for 1, 2, and 4d).[96] This exposure significantly increased stress hormones, blood pressure, endothelial dysfunction, and oxidative stress in both vascular and cerebral systems, primarily from phagocytic nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX-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.[70,96] Importantly, endothelial dysfunction was associated with an up- rather than 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.[97] 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, that play a determining role in exerting cardiovascular damage.[96]

A dysregulation of gene networks in response to noise, identifying potential marker genes associated with noise within the vasculature was also observed. This was accompanied by impaired endothelial and vascular signaling. Among the four most up-regulated genes compared to controls were Zbtb44, Setad4, Ypel2, and Ihh. Conversely, the expression of Sacs, Nbeal1, PTPN4, and NR4A3 transcripts in aortic

tissue was significantly reduced by noise. These genes are linked to TGF-beta signaling, autophagy, growth, matrix metalloprotease regulation, and fibrosis.[96]

Cellular pathway analysis unveiled alterations in NF-κB 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.[70,96]

The central role of nighttime noise, inflammatory cells, and changes in the circadian rhythm

As opposed to the awake phase, exposure 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).[70] Additionally, it resulted in dysregulation of central and peripheral Foxo3/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.[70] Surprisingly, within 4d of continuous noise exposure, noise also triggered a significant downregulation and uncoupling of neuronal nitric oxide synthase (nNOS), creating a neuroinflammatory phenotype, as indicated by markers of inflammation and astrocyte activation.[70] 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.[98]

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,[99] arterial hypertension,[100] and smoking,[101] induce endothelial and vascular dysfunction. This suggests that noise-induced stress and pre-existing 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 pre-existing arterial hypertension (angiotensin-II infused animals, exposed to a continuous Leq of 72 dB(A) and peak levels of 85 dB(A) for 24 hours a day for seven days).[102] 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.[102] In addition, noise with a mean sound pressure level of 72 dB(A) for 4d induced oxidative DNA damage and enhanced NOX-2 expression in C57BL/6 mice.[103] In Ogg1-/- mice (DNA-repair deficient 8-oxoguanine glycosylase 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 4d. 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$^{-/y}$ mice. Noise exposure also induced substantial endothelial dysfunction in cerebral microvessels, associated with higher oxidative stress burden and inflammation, demonstrating a link between a pro-inflammatory 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.[104]

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 28d, revealing a persistent endothelial dysfunction and elevated blood pressure.[105] Additionally, there was a time-dependent increase in formation of ROS, as observed through dihydroethidium (DHE) staining and HPLC-based superoxide measurements in the aorta, heart, and brain. The oxidative burst in whole blood peaked after 4-7d of noise exposure. Increased superoxide in the brain coincided with downregulation of neuronal nitric oxide synthase (Nos3) and the

transcription factor Foxo3 genes. Conversely, Vcam1 mRNA, a marker of inflammation, was upregulated in all noise exposure groups. Endothelial dysfunction and inflammation persisted throughout 28d 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.[105]

Noise preconditioning and myocardial infarction

A significant clinical question concerns whether the side effects of noise are aggravated in vulnerable patients, e.g., 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 4d, activating pro-inflammatory aortic gene expression related to myeloid cell adhesion and diapedesis pathways.[106] Noise exposure promoted adhesion and infiltration of inflammatory myeloid cells in vascular and cardiac tissues, accompanied by increased percentage of leukocytes exhibiting a pro-inflammatory phenotype, characterized by ROS and upregulation of NADPH oxidase type 2 (Nox2) and phosphorylation of nuclear factor 'kappa light chain enhancer' of activated B-cells (phospho-NFκB) in peripheral blood.[106] This pro-inflammatory 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 $CD11b^{+}$ myeloid cells and $Ly6C^{high}$ monocytes into the cardiac tissue, and the induction of IL-6, IL-1β, CCL-2, and Nox2. These effects were intensified when noise exposure had occurred before MI (Figure 5). There was also an increase in mitochondrial $O_2^{\cdot-}$ production due to a reduction in the oxygen consumption rate (OCR). The MI induced more pronounced endothelial dysfunction and increased vascular ROS levels in animals preconditioned with noise.[106] These observations are in accordance with the previous finding that noise-mediated vascular damage was efficiently prevented when pro-inflammatory subsets of myelomonocytic cells were ablated using a genetic mouse model of specific depletion of LysM-positive cells based on LysM-specific overexpression of a diphtheria toxin receptor.[107]

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 C-reactive protein levels at baseline and a more substantial decline in left ventricular ejection fraction (LVEF) after the MI.[106] Accordingly, in a prospective study, persons with verified acute coronary syndromes were found particularly vulnerable to effects from aircraft noise.[108] 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 on humans and animals indicate that CVD patients are highly vulnerable to noise.

How long does the cardiovascular system need to recover after noise stress?

Following a continuous exposure period lasting 4d, the cessation of noise for either 1, 2, or 4d proved sufficient to completely normalize noise-induced endothelial dysfunction in the aorta (in mice).[109] 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 4d 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.[109]

Noise-induced side effects can be modified via non-pharmacological and pharmacological activation of the α1AMPK

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.[110] Also, regular exercise is considered a mean to mitigate the impact of air pollution-induced CVD and mortality.[111]

We recently explored the potential protective effects of α1AMPK activation through exercise, intermittent fasting and pharmacological activation by AICAR (5-aminoimidazole-4-carboxamide riboside) in a murine model of vascular dysfunction-induced aircraft noise.[112] 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 asymmetric dimethylarginine. Importantly, activation of α1AMPK using all three 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 α1AMPK worsened noise-induced vascular damage and nullified the positive effects of exercise or intermittent fasting.[112] These outcomes substantiate that activating endothelium-specific α1AMPK through pharmaceutical stimulation, exercise, and intermittent fasting effectively mitigates noise-induced cardiovascular damage.

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.[113] In support, noise-exposed animals exhibit elevated circulating levels of the neurohormone angiotensin-II (Figure 7).[96,114]

In animals, activation of the sympathetic nervous system due to oxidative stress induced by NADPH oxidase is the connecting link between RAAS-mediated NOX-2 activation and subsequent release of catecholamines.[115,116] Conversely, catecholamines can incite oxidative stress in rats by modulating monoamine oxidase activity or activating astrocytes, microglia, and NOX-2.[117] Consistent with the concept of an RAAS-ROS-SNS axis, administering NADPH oxidase inhibitors reduces blood pressure and levels of angiotensin-II and noradrenaline in hypertensive mice.[118] Furthermore, oxidative stress in the heart and vasculature is mitigated through the blockade of the AT1 receptor and inhibition of the angiotensin-converting enzyme.[119,120]

Aircraft noise triggers an increase in the expression of endothelin-1 in the aorta of mice secondary to increased oxidative stress.[121] Endothelin-1 is a potent

vasoconstrictor and activates NOX-2, which is partially dependent on the RAAS.[70,96,122]

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).

Co-Exposure 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 (DALYs), whereas environmental noise ranks second.[123] Air and noise pollution often share common sources, including aircrafts, 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 50-120 billion EUR, and smoking at 544 billion EUR.[124] Several studies on transportation noise have incorporated mutual adjustment for air pollution. A review from 2023 concluded that air pollution did not appear to confound the association between noise and cardiovascular health, strongly indicating that transportation noise and air pollution independently increase the risk of CVD.[125] The review also concluded that more studies on potential interactions between these two exposures were needed.

To investigate this further, we employed an exposure system with an aerosol generator and loudspeakers, subjecting mice to acute exposure for 3d to ambient particulate matter and/or 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.[126] 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 PM affecting the lungs. The combined impact of both stressors exhibited additive adverse effects on the cardiovascular system, likely driven by PM-induced systemic inflammation and noise-induced stress hormone signaling.[126] These studies also revealed an additive upregulation of ACE-2 in the lungs, potentially explaining the increased vulnerability to COVID-19 infection in populations residing in highly air and noise-polluted areas.[127]

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 PM exposure.[126]

Noise Mitigation Maneuvers

Local authorities can employ various strategies to mitigate the noise from roads, railways, and aircraft. For road traffic, it is important to note that at speeds exceeding 30-35 km/h for cars and 55-65 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, approximately 1 dB(A). Several established strategies can be employed 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 approximately 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 approximately 2-3 dB(A). Since 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 take-offs 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. Nighttime 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 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.

Noise and air pollution are correlated as they are emitted from common sources, most importantly aircrafts, trains, and road vehicles. The estimated costs of co-exposure to noise and air pollution greatly surpass those associated with alcohol and smoking.[124] Consequently, numerous research gaps warrant attention, including the assessment of the magnitude and time course of responses to co-exposure to noise and air pollution, the exploration of the synergistic effects of both exposures on surrogate measures like blood pressure and diabetes, and the determination of the duration of effects and their potential for reversal. There is also a need for investigating the impact of cardiovascular therapies, such as statins, ACE inhibitors,

AT-1 receptor blockers, and AMP-kinase activators, on noise- 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 conspicuously absent from the ESC[110] and the ACC/AHA guidelines for prevention.[128]

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 believe so. Rather we must assess the so-called exposome or individual encounters throughout life and how these exposures impact biology and health.[129] It encompasses external and internal factors, including chemical, physical, biological, and social factors that may influence human health. The exposome will help to predict the risk for future CVD more precisely.

Conflict of Interest

None.

Funding

T.M. and A.D. were supported by vascular biology research grants from the Boehringer Ingelheim Foundation for the collaborative research group "Novel and neglected cardiovascular risk factors: molecular mechanisms and therapeutics" and through continuous research support from Foundation Heart of Mainz. T.M. is PI, and O.H., M.M., M.K., and A.D. are (Young) Scientists of the DZHK (German Center for Cardiovascular Research), Partner Site Rhine-Main, Mainz, Germany. The Umbrella+ review is partly funded by the European Environmental Agency as part of a grant with the European Topic Centre on Human health and the environment (ETC-HE) to Swiss TPH.

References

1. Al-Kindi SG, Brook RD, Biswal S, Rajagopalan S. Environmental determinants of cardiovascular disease: lessons learned from air pollution. *Nat Rev Cardiol*. 2020;17:656-672. doi: 10.1038/s41569-020-0371-2
2. Lelieveld J, Klingmuller K, Pozzer A, Poschl U, Fnais M, Daiber A, Munzel T. Cardiovascular disease burden from ambient air pollution in Europe reassessed using novel hazard ratio functions. *Eur Heart J*. 2019;40:1590-1596. doi: 10.1093/eurheartj/ehz135
3. Sorensen C, Lehmann E, Holder C, Hu J, Krishnan A, Munzel T, Mb R, Rn S. Reducing the health impacts of ambient air pollution. *BMJ*. 2022;379:e069487. doi: 10.1136/bmj-2021-069487
4. Munzel T, Sorensen M, Lelieveld J, Hahad O, Al-Kindi S, Nieuwenhuijsen M, Giles-Corti B, Daiber A, Rajagopalan S. Heart healthy cities: genetics loads the gun but the environment pulls the trigger. *Eur Heart J*. 2021;42:2422-2438. doi: 10.1093/eurheartj/ehab235
5. Basner M, Babisch W, Davis A, Brink M, Clark C, Janssen S, Stansfeld S. Auditory and non-auditory effects of noise on health. *Lancet*. 2014;383:1325-1332. doi: 10.1016/S0140-6736(13)61613-X
6. European Environment Agency. Healthy environment, healthy lives: how the environment influences health and well-being in Europe. *EEA Report NO 21/2019 Luxembourg: Publications Office of the European Union*. 2020.
7. European Environment Agency. Environmental noise in Europe — 2020. https://www.eea.europa.eu/publications/environmental-noise-in-europe (last accessed on 28 December 2020).
8. Hahad O, Beutel M, Gori T, Schulz A, Blettner M, Pfeiffer N, Rostock T, Lackner K, Sorensen M, Prochaska JH, et al. Annoyance to different noise sources is associated with atrial fibrillation in the Gutenberg Health Study. *Int J Cardiol*. 2018;264:79-84. doi: 10.1016/j.ijcard.2018.03.126
9. World Health Organization. Environmental noise guidelines for the European region. *WHO Regional Office for Europe, Copenhagen*. 2018.
10. Babisch W. Stress hormones in the research on cardiovascular effects of noise. *Noise Health*. 2003;5:1-11. doi: NO_DOI
11. Munzel T, Sorensen M, Daiber A. Transportation noise pollution and cardiovascular disease. *Nat Rev Cardiol*. 2021;18:619-636. doi: 10.1038/s41569-021-00532-5
12. Munzel T, Knorr M, Schmidt F, von Bardeleben S, Gori T, Schulz E. Airborne disease: a case of a Takotsubo cardiomyopathie as a consequence of nighttime aircraft noise exposure. *Eur Heart J*. 2016;37:2844. doi: 10.1093/eurheartj/ehw314
13. Osborne MT, Radfar A, Hassan MZO, Abohashem S, Oberfeld B, Patrich T, Tung B, Wang Y, Ishai A, Scott JA, et al. A neurobiological mechanism linking transportation noise to cardiovascular disease in humans. *Eur Heart J*. 2019. doi: 10.1093/eurheartj/ehz820
14. Dar T, Osborne MT, Abohashem S, Abbasi T, Choi KW, Ghoneem A, Naddaf N, Smoller JW, Pitman RK, Denninger JW, et al. Greater Neurobiological Resilience to Chronic Socioeconomic or Environmental Stressors Associates With Lower Risk for

Cardiovascular Disease Events. *Circ Cardiovasc Imaging*. 2020;13:e010337. doi: 10.1161/CIRCIMAGING.119.010337

15. WHO. Environmental noise guidelines for the European Region. In: Organization WH, ed. Copenhagen: WHO Regional Office for Europe; 2018.
16. Engelmann N, Blanes Guàrdia N, Fons Esteve J, Vienneau D, M. R. Environmental noise health risk assessment: methodology for assessing health risks using data reported under the Environmental Noise Directive. In: 2023/X EREH, ed. European Topic Centre on Human Health and the Environment.; in press.
17. van Kempen E, Casas M, Pershagen G, Foraster M. 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*. 2018;15. doi: 10.3390/ijerph15020379
18. Pyko A, Roswall N, Ögren M, Oudin A, Rosengren A, Eriksson C, Segersson D, Rizzuto D, Andersson EM, Aasvang GM, et al. Long-Term Exposure to Transportation Noise and Ischemic Heart Disease: A Pooled Analysis of Nine Scandinavian Cohorts. *Environmental Health Perspectives*. 2023;131:17003. doi: 10.1289/EHP10745
19. Thacher JD, Poulsen AH, Raaschou-Nielsen O, Hvidtfeldt UA, Brandt J, Christensen JH, Khan J, Levin G, Munzel T, Sorensen M. Exposure to transportation noise and risk for cardiovascular disease in a nationwide cohort study from Denmark. *Environ Res*. 2022;211:113106. doi: 10.1016/j.envres.2022.113106
20. Roswall N, Pyko A, Ogren M, Oudin A, Rosengren A, Lager A, Poulsen AH, Eriksson C, Segersson D, Rizzuto D, et al. Long-Term Exposure to Transportation Noise and Risk of Incident Stroke: A Pooled Study of Nine Scandinavian Cohorts. *Environ Health Perspect*. 2021;129:107002. doi: 10.1289/EHP8949
21. Seidler A, Wagner M, Schubert M, Dröge P, Römer K, Pons-Kühnemann J, Swart E, Zeeb H, Hegewald J. Aircraft, road and railway traffic noise as risk factors for heart failure and hypertensive heart disease—A case-control study based on secondary data. *International Journal of Hygiene and Environmental Health*. 2016;219:749-758. doi: 10.1016/j.ijheh.2016.09.012
22. Thacher JD, Poulsen AH, Hvidtfeldt UA, Raaschou-Nielsen O, Ketzel M, Jensen SS, Brandt J, Valencia VH, Münzel T, Sørensen M. Long-term exposure to transportation noise and risk for atrial fibrillation: A Danish nationwide cohort study. *Environmental Research*. 2022;207:112167. doi: 10.1016/j.envres.2021.112167
23. Sorensen M, Poulsen AH, Hvidtfeldt UA, Munzel T, Thacher JD, Ketzel M, Brandt J, Christensen JH, Levin G, Raaschou-Nielsen O. Transportation noise and risk of stroke: a nationwide prospective cohort study covering Denmark. *Int J Epidemiol*. 2021;50:1147-1156. doi: 10.1093/ije/dyab024
24. Pyko A, Roswall N, Ogren M, Oudin A, Rosengren A, Eriksson C, Segersson D, Rizzuto D, Andersson EM, Aasvang GM, et al. Long-Term Exposure to Transportation Noise and Ischemic Heart Disease: A Pooled Analysis of Nine Scandinavian Cohorts. *Environ Health Perspect*. 2023;131:17003. doi: 10.1289/EHP10745
25. Vienneau D, Saucy A, Schaffer B, Fluckiger B, Tangermann L, Stafoggia M, Wunderli JM, Roosli M, group SNCs. Transportation noise exposure and cardiovascular mortality: 15-years of follow-up in a nationwide prospective cohort in Switzerland. *Environ Int*. 2022;158:106974. doi: 10.1016/j.envint.2021.106974
26. Thacher JD, Poulsen AH, Hvidtfeldt UA, Raaschou-Nielsen O, Brandt J, Geels C, Khan J, Munzel T, Sorensen M. Long-Term Exposure to Transportation Noise and Risk for Type

2 Diabetes in a Nationwide Cohort Study from Denmark. *Environ Health Perspect*. 2021;129:127003. doi: 10.1289/EHP9146

27. Sorensen M, Raaschou-Nielsen O, Poulsen AH, Hvidtfeldt UA, Brandt J, Khan J, Jensen SS, Munzel T, Thacher JD. Long-term exposure to residential transportation noise and mortality: A nationwide cohort study. *Environ Pollut*. 2023;328:121642. doi: 10.1016/j.envpol.2023.121642
28. Thacher JD, Poulsen AH, Raaschou-Nielsen O, Jensen A, Hillig K, Roswall N, Hvidtfeldt U, Jensen SS, Levin G, Valencia VH, Sorensen M. High-resolution assessment of road traffic noise exposure in Denmark. *Environ Res*. 2020;182:109051. doi: 10.1016/j.envres.2019.109051
29. Vienneau D, Heritier H, Foraster M, Eze IC, Schaffner E, Thiesse L, Rudzik F, Habermacher M, Kopfli M, Pieren R, et al. Facades, floors and maps - Influence of exposure measurement error on the association between transportation noise and myocardial infarction. *Environ Int*. 2019;123:399-406. doi: 10.1016/j.envint.2018.12.015
30. Sivakumaran K, Ritonja JA, Waseem H, AlShenaibar L, Morgan E, Ahmadi SA, Denning A, Michaud DS, Morgan RL. Impact of Noise Exposure on Risk of Developing Stress-Related Health Effects Related to the Cardiovascular System: A Systematic Review and Meta-Analysis. *Noise Health*. 2022;24:107-129. doi: 10.4103/nah.nah_83_21
31. Nguyen DD, Whitsel EA, Wellenius GA, Levy JI, Leibler JH, Grady ST, Stewart JD, Fox MP, Collins JM, Eliot MN, et al. Long-term aircraft noise exposure and risk of hypertension in postmenopausal women. *Environmental Research*. 2023;218:115037. doi: 10.1016/j.envres.2022.115037
32. Kim CS, Grady ST, Hart JE, Laden F, VoPham T, Nguyen DD, Manson JE, James P, Forman JP, Rexrode KM, et al. Long-term aircraft noise exposure and risk of hypertension in the Nurses' Health Studies. *Environmental Research*. 2022;207:112195. doi: 10.1016/j.envres.2021.112195
33. Buddeke J, Bots ML, van Dis I, Visseren FL, Hollander M, Schellevis FG, Vaartjes I. Comorbidity in patients with cardiovascular disease in primary care: a cohort study with routine healthcare data. *Br J Gen Pract*. 2019;69:e398-e406. doi: 10.3399/bjgp19X702725
34. Powell-Wiley TM, Poirier P, Burke LE, Despres JP, Gordon-Larsen P, Lavie CJ, Lear SA, Ndumele CE, Neeland IJ, Sanders P, et al. Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2021;143:e984-e1010. doi: 10.1161/CIR.0000000000000973
35. Clark C, Sbihi H, Tamburic L, Brauer M, Frank LD, Davies HW. 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*. 2017;125:087025. doi: 10.1289/EHP1279
36. Eze IC, Foraster M, Schaffner E, Vienneau D, Heritier H, Rudzik F, Thiesse L, Pieren R, Imboden M, von Eckardstein A, et al. Long-term exposure to transportation noise and air pollution in relation to incident diabetes in the SAPALDIA study. *Int J Epidemiol*. 2017;46:1115-1125. doi: 10.1093/ije/dyx020
37. Dimakopoulou K, Koutentakis K, Papageorgiou I, Kasdagli MI, Haralabidis AS, Sourtzi P, Samoli E, Houthuijs D, Swart W, Hansell AL, Katsouyanni K. Is aircraft noise exposure associated with cardiovascular disease and hypertension? Results from a cohort study

in Athens, Greece. *Occup Environ Med*. 2017;74:830-837. doi: 10.1136/oemed-2016-104180

38. Roswall N, Raaschou-Nielsen O, Jensen SS, Tjonneland A, Sorensen M. Long-term exposure to residential railway and road traffic noise and risk for diabetes in a Danish cohort. *Environ Res*. 2018;160:292-297. doi: 10.1016/j.envres.2017.10.008
39. Ohlwein S, Hennig F, Lucht S, Matthiessen C, Pundt N, Moebus S, Jöckel KH, Hoffmann B. Indoor and outdoor road traffic noise and incident diabetes mellitus: Results from a longitudinal German cohort study. *Environ Epidemiol*. 2019;3:e037. doi: 10.1097/ee9.0000000000000037
40. Jorgensen JT, Brauner EV, Backalarz C, Laursen JE, Pedersen TH, Jensen SS, Ketzel M, Hertel O, Lophaven SN, Simonsen MK, Andersen ZJ. Long-Term Exposure to Road Traffic Noise and Incidence of Diabetes in the Danish Nurse Cohort. *Environ Health Perspect*. 2019;127:57006. doi: 10.1289/EHP4389
41. Shin S, Bai L, Oiamo TH, Burnett RT, Weichenthal S, Jerrett M, Kwong JC, Goldberg MS, Copes R, Kopp A, Chen H. Association Between Road Traffic Noise and Incidence of Diabetes Mellitus and Hypertension in Toronto, Canada: A Population-Based Cohort Study. *J Am Heart Assoc*. 2020;9:e013021. doi: 10.1161/JAHA.119.013021
42. Liu C, Li W, Chen X, Liu M, Zuo L, Chen L, Chen H, Xu W, Hao G. Dose-response association between transportation noise exposure and type 2 diabetes: A systematic review and meta-analysis of prospective cohort studies. *Diabetes Metab Res Rev*. 2023;39:e3595. doi: 10.1002/dmrr.3595
43. Sorensen M, Hvidtfeldt UA, Poulsen AH, Thygesen LC, Frohn LM, Khan J, Raaschou-Nielsen O. Long-term exposure to transportation noise and risk of type 2 diabetes: A cohort study. *Environ Res*. 2023;217:114795. doi: 10.1016/j.envres.2022.114795
44. Hahad O, Daiber A, Munzel T. Heightened amygdalar activity mediates the cardiometabolic effects of transportation noise stress. *Psychoneuroendocrinology*. 2021;131:105347. doi: 10.1016/j.psyneuen.2021.105347
45. Hahad O, Wild PS, Prochaska JH, Schulz A, Hermanns I, Lackner KJ, Pfeiffer N, Schmidtmann I, Beutel M, Gori T, et al. Endothelial Function Assessed by Digital Volume Plethysmography Predicts the Development and Progression of Type 2 Diabetes Mellitus. *J Am Heart Assoc*. 2019;8:e012509. doi: 10.1161/JAHA.119.012509
46. Christensen JS, Raaschou-Nielsen O, Tjonneland A, Nordsborg RB, Jensen SS, Sorensen TI, Sorensen M. Long-term exposure to residential traffic noise and changes in body weight and waist circumference: A cohort study. *Environ Res*. 2015;143:154-161. doi: 10.1016/j.envres.2015.10.007
47. Pyko A, Eriksson C, Lind T, Mitkovskaya N, Wallas A, Ogren M, Ostenson CG, Pershagen G. Long-Term Exposure to Transportation Noise in Relation to Development of Obesity-a Cohort Study. *Environ Health Perspect*. 2017;125:117005. doi: 10.1289/EHP1910
48. Foraster M, Eze IC, Vienneau D, Schaffner E, Jeong A, Heritier H, Rudzik F, Thiesse L, Pieren R, Brink M, et al. Long-term exposure to transportation noise and its association with adiposity markers and development of obesity. *Environ Int*. 2018;121:879-889. doi: 10.1016/j.envint.2018.09.057
49. Sorensen M, Sorensen TIA, Ketzel M, Raaschou-Nielsen O. Exposure to traffic noise and gestational weight gain and postpartum weight retention: a cohort study. *Occup Environ Med*. 2020;77:107-114. doi: 10.1136/oemed-2019-105843

50. Wallas A, Ekstrom S, Bergstrom A, Eriksson C, Gruzieva O, Sjostrom M, Pyko A, Ogren M, Bottai M, Pershagen G. Traffic noise exposure in relation to adverse birth outcomes and body mass between birth and adolescence. *Environ Res*. 2019;169:362-367. doi: 10.1016/j.envres.2018.11.039
51. Christensen JS, Hjortebjerg D, Raaschou-Nielsen O, Ketzel M, Sorensen TI, Sorensen M. Pregnancy and childhood exposure to residential traffic noise and overweight at 7years of age. *Environ Int*. 2016;94:170-176.
52. Dhar AK, Barton DA. Depression and the Link with Cardiovascular Disease. *Front Psychiatry*. 2016;7:33. doi: 10.3389/fpsyt.2016.00033
53. Hegewald J, Schubert M, Freiberg A, Romero Starke K, Augustin F, Riedel-Heller SG, Zeeb H, Seidler A. Traffic Noise and Mental Health: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health*. 2020;17. doi: 10.3390/ijerph17176175
54. Eze IC, Foraster M, Schaffner E, Vienneau D, Pieren R, Imboden M, Wunderli JM, Cajochen C, Brink M, Röösli M, Probst-Hensch N. Incidence of depression in relation to transportation noise exposure and noise annoyance in the SAPALDIA study. *Environ Int*. 2020;144:106014. doi: 10.1016/j.envint.2020.106014
55. Shi J, Huang J, Guo M, Tian L, Wang J, Wong TW, Webster C, Leung GM, Ni MY. Contributions of residential traffic noise to depression and mental wellbeing in Hong Kong: A prospective cohort study. *Environ Pollut*. 2023;338:122641. doi: 10.1016/j.envpol.2023.122641
56. Wicki B, Schaffer B, Wunderli JM, Muller TJ, Pervilhac C, Roosli M, Vienneau D. Suicide and Transportation Noise: A Prospective Cohort Study from Switzerland. *Environ Health Perspect*. 2023;131:37013. doi: 10.1289/EHP11587
57. Beutel ME, Junger C, Klein EM, Wild P, Lackner K, Blettner M, Binder H, Michal M, Wiltink J, Brahler E, Munzel T. Noise Annoyance Is Associated with Depression and Anxiety in the General Population- The Contribution of Aircraft Noise. *PLoS One*. 2016;11:e0155357. doi: 10.1371/journal.pone.0155357
58. Foraster M, Eze IC, Vienneau D, Brink M, Cajochen C, Caviezel S, Heritier H, Schaffner E, Schindler C, Wanner M, et al. Long-term transportation noise annoyance is associated with subsequent lower levels of physical activity. *Environ Int*. 2016;91:341-349. doi: 10.1016/j.envint.2016.03.011
59. Roswall N, Ammitzboll G, Christensen JS, Raaschou-Nielsen O, Jensen SS, Tjonneland A, Sorensen M. Residential exposure to traffic noise and leisure-time sports - A population-based study. *Int J Hyg Environ Health*. 2017;220:1006-1013. doi: 10.1016/j.ijheh.2017.05.010
60. Roswall N, Christensen JS, Bidstrup PE, Raaschou-Nielsen O, Jensen SS, Tjonneland A, Sorensen M. Associations between residential traffic noise exposure and smoking habits and alcohol consumption-A population-based study. *Environ Pollut*. 2018;236:983-991. doi: 10.1016/j.envpol.2017.10.093
61. Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, Dinges DF, Gangwisch J, Grandner MA, Kushida C, et al. Recommended Amount of Sleep for a Healthy Adult: A Joint Consensus Statement of the American Academy of Sleep Medicine and Sleep Research Society. *Sleep*. 2015;38:843-844. doi: 10.5665/sleep.4716
62. Tobaldini E, Costantino G, Solbiati M, Cogliati C, Kara T, Nobili L, Montano N. Sleep, sleep deprivation, autonomic nervous system and cardiovascular diseases.

Neuroscience and Biobehavioral Reviews. 2017;74:321-329. doi: 10.1016/j.neubiorev.2016.07.004

63. Basner M, Muller U, Elmenhorst EM. Single and combined effects of air, road, and rail traffic noise on sleep and recuperation. *Sleep*. 2011;34:11-23. doi: 10.1093/sleep/34.1.11

64. Basner M, Babisch W, Davis A, Brink M, Clark C, Janssen S, Stansfeld S. Auditory and non-auditory effects of noise on health. *Lancet*. 2014;383:1325-1332. doi: 10.1016/S0140-6736(13)61613-X

65. Thiesse L, Rudzik F, Kraemer JF, Spiegel K, Leproult R, Wessel N, Pieren R, Heritier H, Eze IC, Foraster M, et al. Transportation noise impairs cardiovascular function without altering sleep: The importance of autonomic arousals. *Environ Res*. 2020;182:109086. doi: 10.1016/j.envres.2019.109086

66. Jarup L, Babisch W, Houthuijs D, Pershagen G, Katsouyanni K, Cadum E, Dudley ML, Savigny P, Seiffert I, Swart W, et al. Hypertension and exposure to noise near airports: the HYENA study. *Environmental Health Perspectives*. 2008;116:329-333.

67. Schmidt F, Kolle K, Kreuder K, Schnorbus B, Wild P, Hechtner M, Binder H, Gori T, Munzel T. Nighttime aircraft noise impairs endothelial function and increases blood pressure in patients with or at high risk for coronary artery disease. *Clin Res Cardiol*. 2015;104:23-30. doi: 10.1007/s00392-014-0751-x

68. Münzel T, Kröller-Schön S, Oelze M, Gori T, Schmidt FP, Steven S, Hahad O, Röösli M, Wunderli J-M, Daiber A, Sørensen M. Adverse Cardiovascular Effects of Traffic Noise with a Focus on Nighttime Noise and the New WHO Noise Guidelines. *Annual Review of Public Health*. 2020;41:309-328. doi: 10.1146/annurev-publhealth-081519-062400

69. Haralabidis AS, Dimakopoulou K, Vigna-Taglianti F, Giampaolo M, Borgini A, Dudley ML, Pershagen G, Bluhm G, Houthuijs D, Babisch W, et al. Acute effects of night-time noise exposure on blood pressure in populations living near airports. *Eur Heart J*. 2008;29:658-664. doi: 10.1093/eurheartj/ehn013

70. Kroller-Schon S, Daiber A, Steven S, Oelze M, Frenis K, Kalinovic S, Heimann A, Schmidt FP, Pinto A, Kvandova M, et al. Crucial role for Nox2 and sleep deprivation in aircraft noise-induced vascular and cerebral oxidative stress, inflammation, and gene regulation. *Eur Heart J*. 2018;39:3528-3539. doi: 10.1093/eurheartj/ehy333

71. Saucy A, Schaffer B, Tangermann L, Vienneau D, Wunderli JM, Roosli M. Does night-time aircraft noise trigger mortality? A case-crossover study on 24 886 cardiovascular deaths. *Eur Heart J*. 2021;42:835-843. doi: 10.1093/eurheartj/ehaa957

72. ISO/IEC. ISO/TS 15666:2021 Acoustics — Assessment of noise annoyance by means of social and socio-acoustic surveys. In; 2021.

73. Clark C, Gjestland T, Lavia L, Notley H, Michaud D, Morinaga M. Assessing community noise annoyance: A review of two decades of the international technical specification ISO/TS 15666:2003. *The Journal of the Acoustical Society of America*. 2021;150:3362-3373. doi: 10.1121/10.0006967

74. Guski R. Personal and social variables as co-determinants of noise annoyance. *Noise Health*. 1999;1:45-56.

75. Guski R, Schreckenberg D, Schuemer R. WHO Environmental Noise Guidelines for the European Region: A systematic review on environmental noise and annoyance. *International Journal of Environmental Research and Public Health*. 2017;14:1539.

76. Brink M, Schaffer B, Vienneau D, Foraster M, Pieren R, Eze IC, Cajochen C, Probst-Hensch N, Roosli M, Wunderli JM. A survey on exposure-response relationships for

road, rail, and aircraft noise annoyance: Differences between continuous and intermittent noise. *Environ Int*. 2019;125:277-290. doi: 10.1016/j.envint.2019.01.043
77. Gjestland T. On the Temporal Stability of People's Annoyance with Road Traffic Noise. *International Journal of Environmental Research and Public Health*. 2020;17:1374. doi: 10.3390/ijerph17041374
78. Peeters I, Nusselder R. Overview of critical noise values in the European Region. In: European Network of the Heads of Environment Protection Agencies (EPA Network); 2019.
79. Kryter KD. Evaluation of exposures to impulse noise. *Arch Environ Health*. 1970;20:624-635. doi: 10.1080/00039896.1970.10665675
80. Jansen G. [the Effect of Noise during Physical Work]. *Int Z Angew Physiol*. 1964;20:233-239.
81. Jansen G, Klensch H. [Alteration of the Ballistogram by Sound Impressions and by Music]. *Int Z Angew Physiol*. 1964;20:258-270.
82. Jansen G. Effects of noise on health. *Ger Med Mon*. 1968;13:446-448.
83. Babisch W, Ising H, Gallacher JE, Sharp DS, Baker IA. Traffic noise and cardiovascular risk: the Speedwell study, first phase. Outdoor noise levels and risk factors. *Arch Environ Health*. 1993;48:401-405. doi: 10.1080/00039896.1993.10545961
84. Lusk SL, Gillespie B, Hagerty BM, Ziemba RA. Acute effects of noise on blood pressure and heart rate. *Arch Environ Health*. 2004;59:392-399. doi: 10.3200/AEOH.59.8.392-399
85. Dratva J, Phuleria HC, Foraster M, Gaspoz J-M, Keidel D, Künzli N, Liu LJS, Pons M, Zemp E, Gerbase MW, Schindler C. Transportation Noise and Blood Pressure in a Population-Based Sample of Adults. *Environ Health Perspect*. 2011;120.
86. Bagheri Hosseinabadi M, Khanjani N, Munzel T, Daiber A, Yaghmorloo M. Chronic occupational noise exposure: Effects on DNA damage, blood pressure, and serum biochemistry. *Mutat Res*. 2019;841:17-22. doi: 10.1016/j.mrgentox.2019.04.006
87. Schmidt FP, Basner M, Kroger G, Weck S, Schnorbus B, Muttray A, Sariyar M, Binder H, Gori T, Warnholtz A, Munzel T. Effect of nighttime aircraft noise exposure on endothelial function and stress hormone release in healthy adults. *Eur Heart J*. 2013;34:3508-3514a. doi: 10.1093/eurheartj/eht269
88. Herzog J, Schmidt FP, Hahad O, Mahmoudpour SH, Mangold AK, Garcia Andreo P, Prochaska J, Koeck T, Wild PS, Sorensen M, et al. Acute exposure to nocturnal train noise induces endothelial dysfunction and pro-thromboinflammatory changes of the plasma proteome in healthy subjects. *Basic Res Cardiol*. 2019;114:46. doi: 10.1007/s00395-019-0753-y
89. Schmidt FP, Herzog J, Schnorbus B, Ostad MA, Lasetzki L, Hahad O, Schafers G, Gori T, Sorensen M, Daiber A, Munzel T. The impact of aircraft noise on vascular and cardiac function in relation to noise event number: a randomized trial. *Cardiovasc Res*. 2021;117:1382-1390. doi: 10.1093/cvr/cvaa204
90. Cai Y, Hansell AL, Blangiardo M, Burton PR, BioShaRe, de Hoogh K, Doiron D, Fortier I, Gulliver J, Hveem K, et al. Long-term exposure to road traffic noise, ambient air pollution, and cardiovascular risk factors in the HUNT and lifelines cohorts. *Eur Heart J*. 2017;38:2290-2296. doi: 10.1093/eurheartj/ehx263
91. Kim A, Sung JH, Bang JH, Cho SW, Lee J, Sim CS. Effects of self-reported sensitivity and road-traffic noise levels on the immune system. *PLoS One*. 2017;12:e0187084. doi: 10.1371/journal.pone.0187084

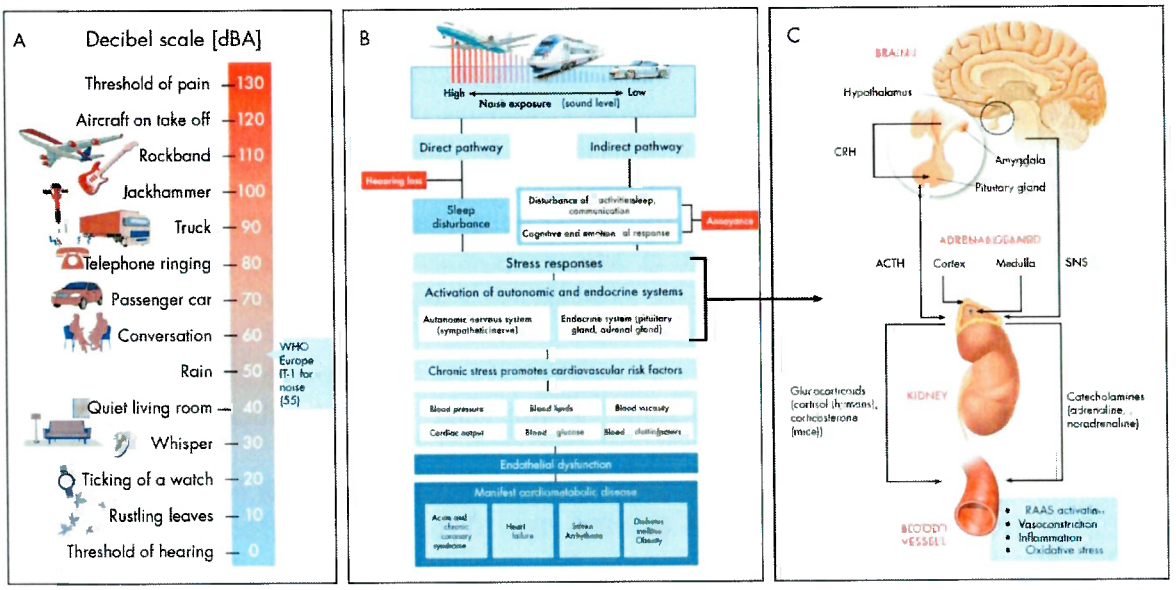
92. Eze IC, Jeong A, Schaffner E, Rezwan FI, Ghantous A, Foraster M, Vienneau D, Kronenberg F, Herceg Z, Vineis P, et al. Genome-Wide DNA Methylation in Peripheral Blood and Long-Term Exposure to Source-Specific Transportation Noise and Air Pollution: The SAPALDIA Study. *Environ Health Perspect*. 2020;128:67003. doi: 10.1289/EHP6174
93. Foraster M, Eze IC, Schaffner E, Vienneau D, Heritier H, Endes S, Rudzik F, Thiesse L, Pieren R, Schindler C, et al. Exposure to Road, Railway, and Aircraft Noise and Arterial Stiffness in the SAPALDIA Study: Annual Average Noise Levels and Temporal Noise Characteristics. *Environ Health Perspect*. 2017;125:097004. doi: 10.1289/EHP1136
94. Kalsch H, Hennig F, Moebus S, Mohlenkamp S, Dragano N, Jakobs H, Memmesheimer M, Erbel R, Jockel KH, Hoffmann B, Heinz Nixdorf Recall Study Investigative G. Are air pollution and traffic noise independently associated with atherosclerosis: the Heinz Nixdorf Recall Study. *Eur Heart J*. 2014;35:853-860. doi: 10.1093/eurheartj/eht426
95. Hennig F, Moebus S, Reinsch N, Budde T, Erbel R, Jockel KH, Lehmann N, Hoffmann B, Kalsch H, Heinz Nixdorf Recall Study Investigative G. Investigation of air pollution and noise on progression of thoracic aortic calcification: results of the Heinz Nixdorf Recall Study. *Eur J Prev Cardiol*. 2020;27:965-974. doi: 10.1177/2047487319854818
96. Munzel T, Daiber A, Steven S, Tran LP, Ullmann E, Kossmann S, Schmidt FP, Oelze M, Xia N, Li H, et al. Effects of noise on vascular function, oxidative stress, and inflammation: mechanistic insight from studies in mice. *Eur Heart J*. 2017;38:2838-2849. doi: 10.1093/eurheartj/ehx081
97. Chen CA, Wang TY, Varadharaj S, Reyes LA, Hemann C, Talukder MA, Chen YR, Druhan LJ, Zweier JL. S-glutathionylation uncouples eNOS and regulates its cellular and vascular function. *Nature*. 2010;468:1115-1118. doi: 10.1038/nature09599
98. Stansfeld SA, Berglund B, Clark C, Lopez-Barrio I, Fischer P, Ohrstrom E, Haines MM, Head J, Hygge S, van Kamp I, et al. Aircraft and road traffic noise and children's cognition and health: a cross-national study. *The Lancet*. 2005;365:1942-1949. doi: 10.1016/S0140-6736(05)66660-3
99. Hink U, Li H, Mollnau H, Oelze M, Matheis E, Hartmann M, Skatchkov M, Thaiss F, Stahl RA, Warnholtz A, et al. Mechanisms underlying endothelial dysfunction in diabetes mellitus. *Circ Res*. 2001;88:E14-22. doi: 10.1161/01.res.88.2.e14
100. Mollnau H, Wendt M, Szocs K, Lassegue B, Schulz E, Oelze M, Li H, Bodenschatz M, August M, Kleschyov AL, et al. Effects of angiotensin II infusion on the expression and function of NAD(P)H oxidase and components of nitric oxide/cGMP signaling. *Circ Res*. 2002;90:E58-65. doi: 10.1161/01.res.0000012569.55432.02
101. Heitzer T, Brockhoff C, Mayer B, Warnholtz A, Mollnau H, Henne S, Meinertz T, Munzel T. Tetrahydrobiopterin improves endothelium-dependent vasodilation in chronic smokers : evidence for a dysfunctional nitric oxide synthase. *Circ Res*. 2000;86:E36-41. doi: 10.1161/01.res.86.2.e36
102. Steven S, Frenis K, Kalinovic S, Kvandova M, Oelze M, Helmstadter J, Hahad O, Filippou K, Kus K, Trevisan C, et al. Exacerbation of adverse cardiovascular effects of aircraft noise in an animal model of arterial hypertension. *Redox Biol*. 2020:101515. doi: 10.1016/j.redox.2020.101515
103. Kvandova M, Filippou K, Steven S, Oelze M, Kalinovic S, Stamm P, Frenis K, Vujacic-Mirski K, Sakumi K, Nakabeppu Y, et al. Environmental aircraft noise aggravates oxidative DNA damage, granulocyte oxidative burst and nitrate resistance in Ogg1(-/-) mice. *Free radical research*. 2020;54:280-292. doi: 10.1080/10715762.2020.1754410

104. Eckrich J, Frenis K, Rodriguez-Blanco G, Ruan Y, Jiang S, Bayo Jimenez MT, Kuntic M, Oelze M, Hahad O, Li H, et al. Aircraft noise exposure drives the activation of white blood cells and induces microvascular dysfunction in mice. *Redox Biol.* 2021;46:102063. doi: 10.1016/j.redox.2021.102063
105. Frenis K, Kalinovic S, Ernst BP, Kvandova M, Al Zuabi A, Kuntic M, Oelze M, Stamm P, Bayo Jimenez MT, Kij A, et al. Long-Term Effects of Aircraft Noise Exposure on Vascular Oxidative Stress, Endothelial Function and Blood Pressure: No Evidence for Adaptation or Tolerance Development. *Front Mol Biosci.* 2021;8:814921. doi: 10.3389/fmolb.2021.814921
106. Molitor M, Jimenez MTB, Hahad O, Witzler C, Finger S, Garlapati VS, Rajlic S, Knopp T, Bieler T, Aluia M, et al. Aircraft noise exposure induces pro-inflammatory vascular conditioning and amplifies vascular dysfunction and impairment of cardiac function after myocardial infarction. *Cardiovasc Res.* 2023. doi: 10.1093/cvr/cvad021
107. Frenis K, Helmstadter J, Ruan Y, Schramm E, Kalinovic S, Kroller-Schon S, Bayo Jimenez MT, Hahad O, Oelze M, Jiang S, et al. Ablation of lysozyme M-positive cells prevents aircraft noise-induced vascular damage without improving cerebral side effects. *Basic Res Cardiol.* 2021;116:31. doi: 10.1007/s00395-021-00869-5
108. Olbrich HG, Roosli M, Herrmann E, Maschke C, Schadow K, Hahnel T, Rupprecht HJ, Kaltenbach M. Aircraft noise exposure and risk for recurrent cardiovascular events after acute coronary syndrome: A prospective patient cohort study. *Environ Res.* 2023;238:117108. doi: 10.1016/j.envres.2023.117108
109. Bayo Jimenez MT, Gericke A, Frenis K, Rajlic S, Kvandova M, Kroller-Schon S, Oelze M, Kuntic M, Kuntic I, Mihalikova D, et al. Effects of aircraft noise cessation on blood pressure, cardio- and cerebrovascular endothelial function, oxidative stress, and inflammation in an experimental animal model. *Sci Total Environ.* 2023;903:166106. doi: 10.1016/j.scitotenv.2023.166106
110. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Back M, Benetos A, Biffi A, Boavida JM, Capodanno D, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J.* 2021;42:3227-3337. doi: 10.1093/eurheartj/ehab484
111. Munzel T, Hahad O, Daiber A. Running in polluted air is a two-edged sword - physical exercise in low air pollution areas is cardioprotective but detrimental for the heart in high air pollution areas. *Eur Heart J.* 2021;42:2498-2500. doi: 10.1093/eurheartj/ehab227
112. Kvandova M, Rajlic S, Stamm P, Schmal I, Mihalikova D, Kuntic M, Bayo Jimenez MT, Hahad O, Kollarova M, Ubbens H, et al. Mitigation of aircraft noise-induced vascular dysfunction and oxidative stress by exercise, fasting, and pharmacological alpha1AMPK activation: molecular proof of a protective key role of endothelial alpha1AMPK against environmental noise exposure. *Eur J Prev Cardiol.* 2023. doi: 10.1093/eurjpc/zwad075
113. Schiavone S, Jaquet V, Trabace L, Krause KH. Severe life stress and oxidative stress in the brain: from animal models to human pathology. *Antioxid Redox Signal.* 2013;18:1475-1490. doi: 10.1089/ars.2012.4720
114. Wright JW, Dengerink HA, Miller JM, Goodwin PC. Potential role of angiotensin II in noise-induced increases in inner ear blood flow. *Hear Res.* 1985;17:41-46. doi: 10.1016/0378-5955(85)90128-5

115. Lob HE, Marvar PJ, Guzik TJ, Sharma S, McCann LA, Weyand C, Gordon FJ, Harrison DG. Induction of hypertension and peripheral inflammation by reduction of extracellular superoxide dismutase in the central nervous system. *Hypertension*. 2010;55:277-283, 276p following 283. doi: 10.1161/HYPERTENSIONAHA.109.142646
116. Ye S, Zhong H, Yanamadala S, Campese VM. Oxidative stress mediates the stimulation of sympathetic nerve activity in the phenol renal injury model of hypertension. *Hypertension*. 2006;48:309-315. doi: 10.1161/01.HYP.0000231307.69761.2e
117. Lee HY, Lee JS, Kim HG, Kim WY, Lee SB, Choi YH, Son CG. The ethanol extract of Aquilariae Lignum ameliorates hippocampal oxidative stress in a repeated restraint stress mouse model. *BMC Complement Altern Med*. 2017;17:397. doi: 10.1186/s12906-017-1902-1
118. Grande MT, Pascual G, Riolobos AS, Clemente-Lorenzo M, Bardaji B, Barreiro L, Tornavaca O, Meseguer A, Lopez-Novoa JM. Increased oxidative stress, the renin-angiotensin system, and sympathetic overactivation induce hypertension in kidney androgen-regulated protein transgenic mice. *Free Radic Biol Med*. 2011;51:1831-1841. doi: 10.1016/j.freeradbiomed.2011.08.014
119. Mollnau H, Oelze M, August M, Wendt M, Daiber A, Schulz E, Baldus S, Kleschyov AL, Materne A, Wenzel P, et al. Mechanisms of increased vascular superoxide production in an experimental model of idiopathic dilated cardiomyopathy. *Arterioscler Thromb Vasc Biol*. 2005;25:2554-2559.
120. Rajagopalan S, Kurz S, Munzel T, Tarpey M, Freeman BA, Griendling KK, Harrison DG. 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*. 1996;97:1916-1923. doi: 10.1172/JCI118623
121. Kahler J, Ewert A, Weckmuller J, Stobbe S, Mittmann C, Koster R, Paul M, Meinertz T, Munzel T. Oxidative stress increases endothelin-1 synthesis in human coronary artery smooth muscle cells. *J Cardiovasc Pharmacol*. 2001;38:49-57.
122. Chen DD, Dong YG, Yuan H, Chen AF. Endothelin 1 activation of endothelin A receptor/NADPH oxidase pathway and diminished antioxidants critically contribute to endothelial progenitor cell reduction and dysfunction in salt-sensitive hypertension. *Hypertension*. 2012;59:1037-1043. doi: 10.1161/HYPERTENSIONAHA.111.183368
123. Stansfeld SA. Noise Effects on Health in the Context of Air Pollution Exposure. *Int J Environ Res Public Health*. 2015;12:12735-12760. doi: 10.3390/ijerph121012735
124. Science for environment policy: In depth report 13. The link between noise and air pollution and the socioeconomic status https://ec.europa.eu/environment/integration/research/newsalert/pdf/air_noise_pollution_socioeconomic_status_links_IR13_en.pdf.
125. Eminson K, Cai YS, Chen Y, Blackmore C, Rodgers G, Jones N, Gulliver J, Fenech B, Hansell AL. Does air pollution confound associations between environmental noise and cardiovascular outcomes? - A systematic review. *Environ Res*. 2023;232:116075. doi: 10.1016/j.envres.2023.116075
126. Kuntic M, Kuntic I, Krishnankutty R, Gericke A, Oelze M, Junglas T, Bayo Jimenez MT, Stamm P, Nandudu M, Hahad O, et al. Co-exposure to urban particulate matter and aircraft noise adversely impacts the cerebro-pulmonary-cardiovascular axis in mice. *Redox Biol*. 2023;59:102580. doi: 10.1016/j.redox.2022.102580

127. Pozzer A, Dominici F, Haines A, Witt C, Munzel T, Lelieveld J. Regional and global contributions of air pollution to risk of death from COVID-19. *Cardiovasc Res*. 2020;116:2247-2253. doi: 10.1093/cvr/cvaa288
128. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e596-e646. doi: 10.1161/CIR.0000000000000678
129. Munzel T, Sorensen M, Hahad O, Nieuwenhuijsen M, Daiber A. The contribution of the exposome to the burden of cardiovascular disease. *Nat Rev Cardiol*. 2023. doi: 10.1038/s41569-023-00873-3
130. Munzel T, Schmidt FP, Steven S, Herzog J, Daiber A, Sorensen M. Environmental Noise and the Cardiovascular System. *J Am Coll Cardiol*. 2018;71:688-697. doi: 10.1016/j.jacc.2017.12.015
131. Munzel T, Gori T, Babisch W, Basner M. Cardiovascular effects of environmental noise exposure. *Eur Heart J*. 2014;35:829-836. doi: 10.1093/eurheartj/ehu030
132. Thacher JD, Hvidtfeldt UA, Poulsen AH, Raaschou-Nielsen O, Ketzel M, Brandt J, Jensen SS, Overvad K, Tjonneland A, Munzel T, Sorensen M. Long-term residential road traffic noise and mortality in a Danish cohort. *Environ Res*. 2020;187:109633. doi: 10.1016/j.envres.2020.109633
133. FOEN. sonBASE GIS noise database. Federal Office for the Environment. 2023. Accessed 23.11.2023.

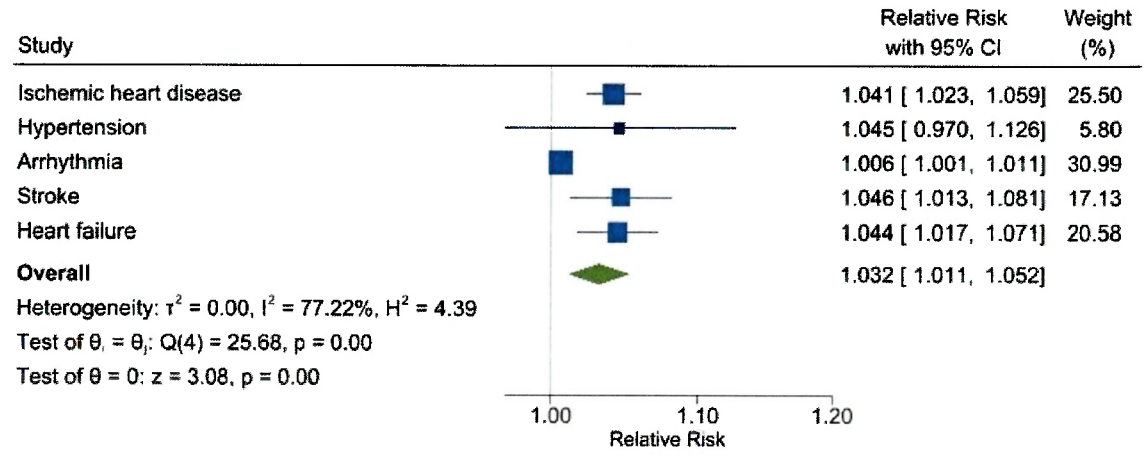
Figure 1



A: Sound pressure levels (SPLs) of different noise sources.[130]
B: Noise reaction model for noise exposure's direct (auditory) and indirect (non-auditory) effects.[131]
C: Neuronal activation (arousals) induced by noise triggers signaling via the hypothalamic–pituitary–adrenal axis and sympathetic nervous system (SNS). This lead to release of corticotropin-releasing hormone from the hypothalamus into the pituitary gland, which stimulates the release of adrenocorticotropic 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 (RAAS) system, and increased inflammation and oxidative stress. Panel A reprinted from [130] with permission. Copyright © 2018 The Authors. Panel B and C adapted from [11] with permission. Copyright © 2021, Springer Nature Limited.

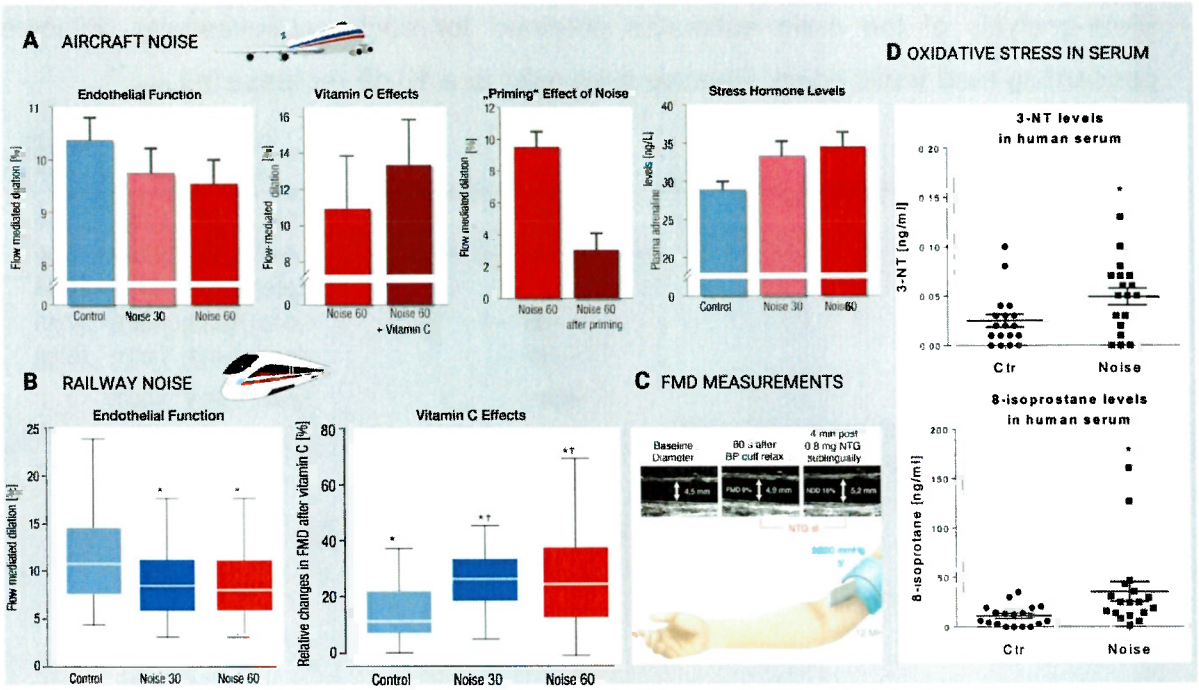
Figure 2

Meta-analysis of the main estimates obtained for each cardiovascular outcome concerning road traffic noise. Relative risks refer to a 10 dB increase in L_{den}.[16]



Random-effects REML model

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, i.e., previous exposure to Noise30 caused Noise60 to have a significantly stronger reduction of flow-mediated dilation [87]. 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. C. Methodology of FMD. D. Effects of aircraft noise on oxidative stress markers (3-nitrotyrosine [3-NT] and 8-isoprostane) in serum that were measured in the samples of the aircraft noise study and published in [70]. Adapted from [70] with permission. Copyright ©2018, Oxford University Press.

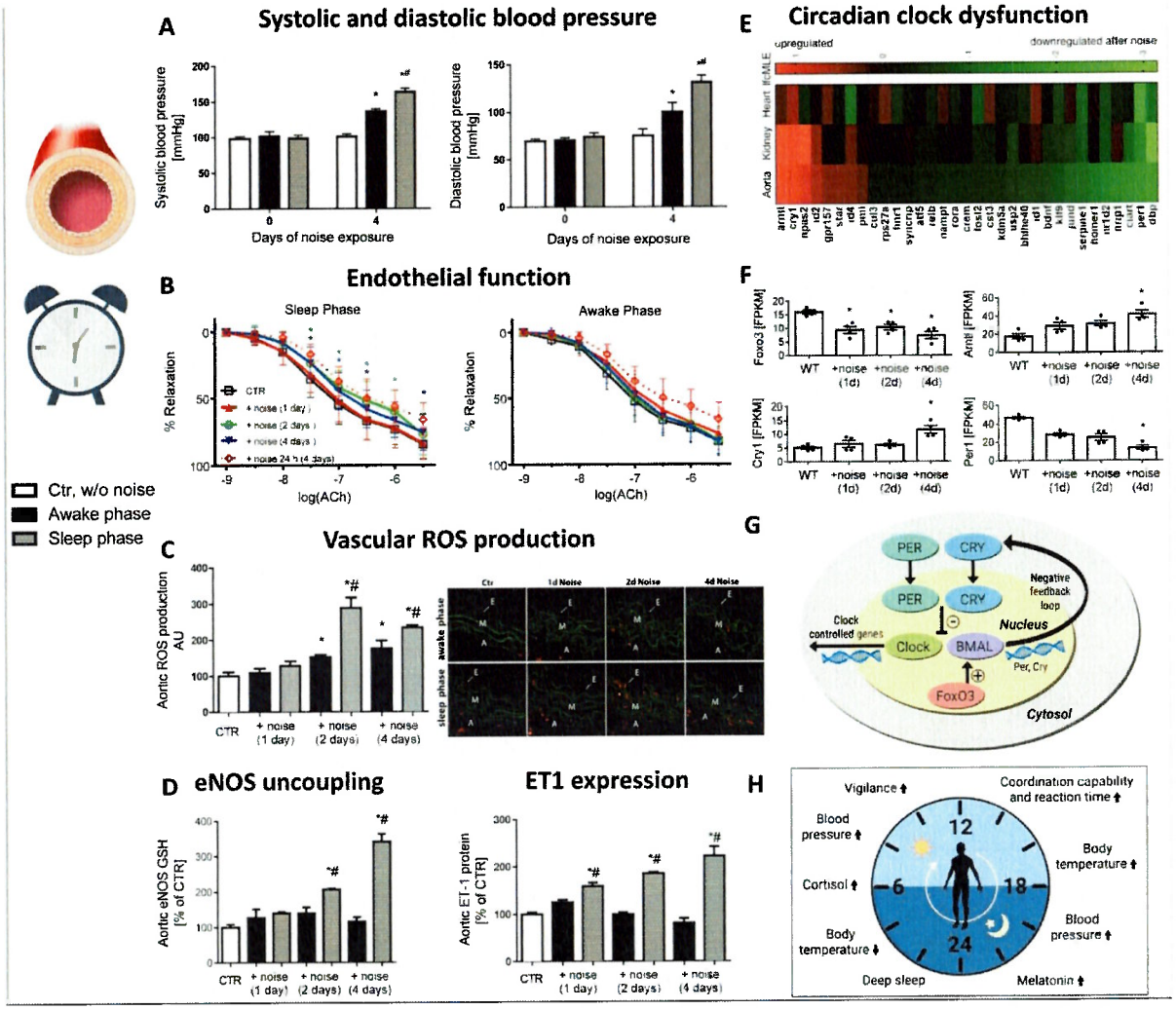
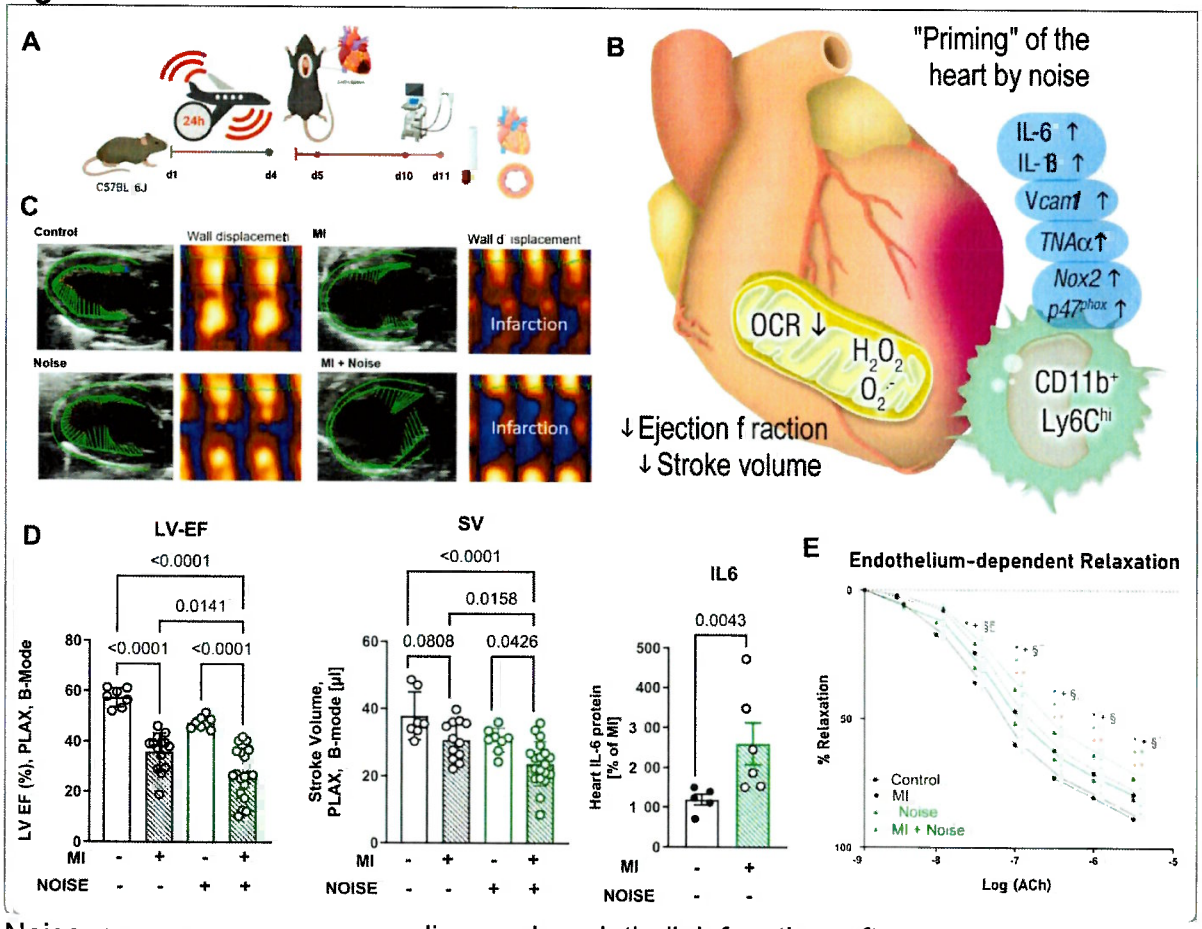


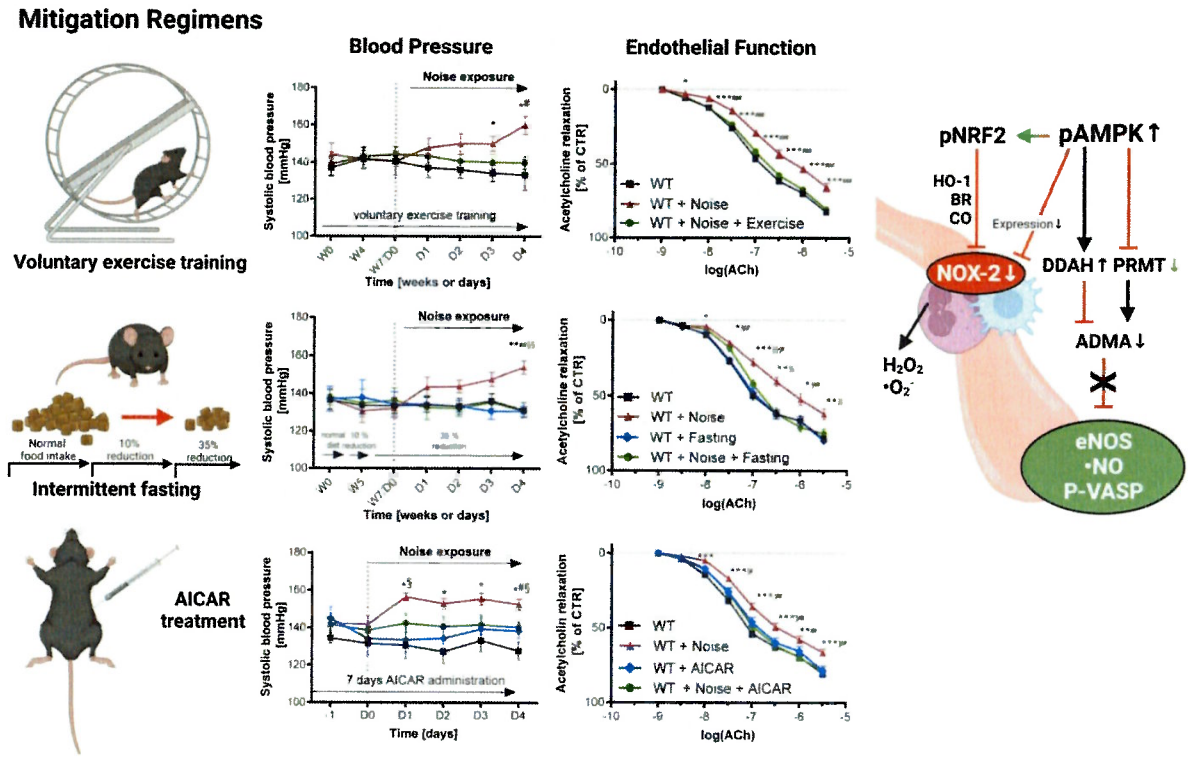
Figure 4 Effects of sleep and awake phase aircraft noise [mean sound pressure level 72 dB(A) for 12 h per day for 1, 2, and 4 days] on the murine vasculature. Sleep phase noise showed a more pronounced increase in systolic and diastolic blood pressure (A) and caused significant endothelial dysfunction (diminished response to acetylcholine [ACh]) (B). For comparison, the impaired endothelium-dependent relaxation in response to 24 h noise exposure is shown in dotted line. Sleep phase noise induced more vascular oxidative stress (red fluorescence staining by oxidized hydroethidium in aortic cryo sections) (C), eNOS uncoupling by immunostaining against S-glutathionylated (= uncoupled) enzyme (eNOS-GSH) and endothelin-1 (ET-1) protein expression by immunohistochemistry (D). Sleep phase noise also caused substantial dysregulation of expression of circadian clock genes in the aorta and kidney as revealed by Illumina RNA sequencing (E). Aortic gene expression of the transcription factor Foxo3 (regulates BMAL1) and period-1 (Per1) were down-regulated. In contrast, brain and muscle aryl hydrocarbon receptor nuclear translocator (Arnt)-like (Bmal) 1 and cryptochrome-1 (Cry1) were up-regulated (F). 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 (G). The circadian clock regulates several essential biological functions (H). Adapted from [70] (A-F) and [68] (G-H) with permission. Copyright ©2018, Oxford University Press and Copyright © 2020 by Annual Reviews.

Figure 5



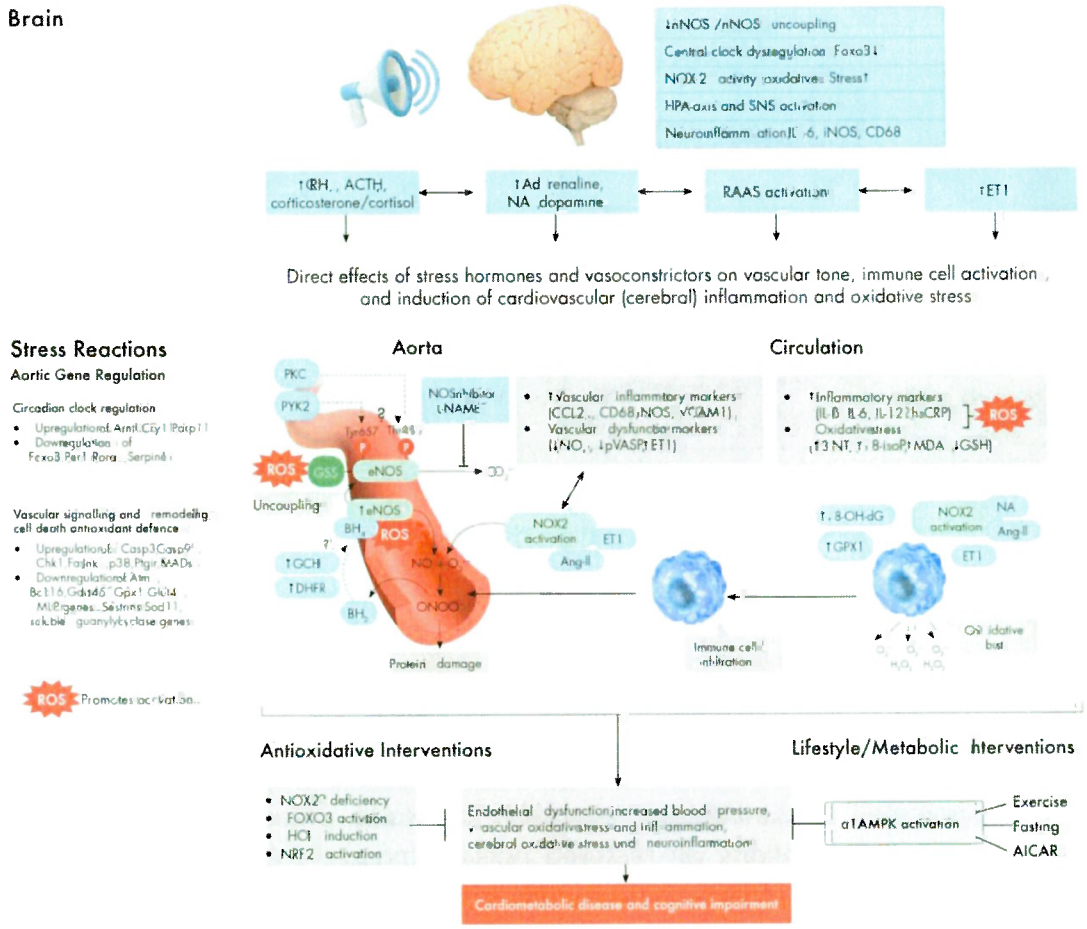
Noise exposure worsens cardiac and endothelial function after acute myocardial infarction (MI). (A) Experimental study scheme with noise exposure before experimental MI by LAD ligation, followed by delayed echocardiography. (B) Noise exposure induces an inflammatory and pro-oxidative phenotype of the heart promoting exacerbation of impaired cardiac function and decreased oxygen consumption rate (OCR) leading to increased mitochondrial production of reactive 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 6d after permanent LAD-ligation or sham operation with or without noise exposure revealed additively decreased left-ventricular ejection fraction (LV-EF in %) and stroke volume (SV in µl). Increased cardiac IL-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. Adapted from [106] with permission. Copyright © 2023 European Society of Cardiology.

Figure 6



Exercise, caloric restriction, and AICAR (5-aminoimidazole-4-carboxamide riboside) 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 three interventions. The proposed protective mechanism of the three mitigation regimens is the activation of α1AMPK leading downstream to an increase of the dimethylarginine dimethylaminohydrolase (DDAH), the degrading enzyme of asymmetric 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 inhibitor, and thereby to more efficient nitric oxide signaling, all of which prevents noise-induced endothelial dysfunction. Activation of α1AMPK also prevents noise-triggered NOX-2 expression / activation and oxidative stress, in part by cross-activation of NRF2 via specific phosphorylation and subsequent heme oxygenase-1 (HO-1) induction followed by carbon monoxide (CO) and bilirubin (BR) production. Adapted from [112] with permission. Copyright © 2023 European Society of Cardiology.

Figure 7



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

Abbreviations:

HPA, hypothalamic-pituitary–adrenal; SNS, sympathetic nervous system; RAAS, renin–angiotensin–aldosterone system; Ang-II, angiotensin-II; ET1, endothelin-1; NOX2, nicotine adenine dinucleotide phosphate oxidase isoform 2 (phagocytic NADPH oxidase); nNOS, neuronal nitric oxide synthase. FOXO3, forkhead box protein O; iNOS, inducible nitric oxide synthase; eNOS, endothelial nitric oxide synthase; $O_2^{\bullet-}$, superoxide; $ONOO^-$, peroxynitrite; BH_4, tetrahydrobiopterin; GSS-, S-glutathionylation; GSH, glutathione; 8-OH-dG, 8-oxo-2'-deoxyguanine; GPX1, glutathione peroxidase 1; AICAR, 5-aminoimidazole-4-carboxamide riboside; 3-NT, 3-nitrotyrosine; 8-isoP: 8-isoprostane; IL, interleukin; CD68, cluster of differentiation 68 (macrosialin); ACTH: adrenocorticotropic hormone; BH_2, dihydrobiopterin; CCL2, CC-chemokine ligand 2; CRH, corticotropin-releasing hormone; DHFR, dihydrofolate reductase; GCH1, GTP cyclohydrolase 1; HO-1, heme oxygenase-1; NRF2, nuclear factor erythroid 2-related factor 2; α1AMPK, alpha1 subunit of adenosine monophosphate-activated protein kinase; GFAP, glial fibrillary acid protein; H_2O_2, hydrogen peroxide; hsCRP, high-sensitivity C-reactive protein; MDA,

malondialdehyde; NA, noradrenaline; pVASP, phosphorylated vasodilator-stimulated phosphoprotein; L-NAME, N^G-nitro-L-arginine methylester; PKC, protein kinase C; PYK2, protein-tyrosine kinase 2; VCAM1 vascular cell adhesion molecule; ROS, reactive oxygen species. Adapted from [11] with permission. Copyright © 2021, Springer Nature Limited.

Table 1
Estimated number of persons who died and/or had an incident ischemic heart disease (IHD) due to exposure to road traffic noise in Denmark and Switzerland. The lower effect threshold of road traffic noise, corresponding the level below which no health effects of noise is expected, is presently unknown, and therefore numbers are estimated for four "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.[132,133]

Lower effect threshold (Lden)	Denmark (5.75 million)		Switzerland (8.48 million)	
	Cardiovascular mortality[1]	IHD incidence[2]	Cardiovascular mortality[1]	IHD incidence[2]
55 dB	206	256	166	291
53 dB	270	336	234	412
50 dB	385	478	371	651
45 dB	616	764	688	1207

[1] Population Attributable Fraction (PAF) estimated using a relative risk of 1.045 for CVD mortality and proportion of people in different noise categories. Number of persons with CVD mortality calculated as PAF*CVD mortality in Denmark (N=12,455, 2017) and Switzerland (N=19,645, 2021), respectively.
[2] Population Attributable Fraction (PAF) estimated using a relative risk of 1.041 for ischemic heart disease (IHD) and proportion of people in different noise categories. Number of persons with incident IHD calculated as PAF*IHD in Denmark (N=16,984, 2017) and Switzerland (N=37,878, 2021), respectively.

Journal of Exposure Science & Environmental Epidemiology www.nature.com/jes

PERSPECTIVE OPEN

Check for updates

Noise causes cardiovascular disease: it's time to act

Thomas Münzel[1,2,3]✉, Andreas Daiber[1,2,3], Nicole Engelmann[4,5], Martin Röösli[4,5], Marin Kuntic[1,2] and Jamie L. Banks[6]

BACKGROUND: Chronic transportation noise is an environmental stressor affecting a substantial portion of the population. The World Health Organization (WHO) and various studies have established associations between transportation noise and cardiovascular disease (CVD), such as myocardial infarction, stroke, heart failure, and arrhythmia. The WHO Environmental Noise Guidelines and recent reviews confirm a heightened risk of cardiovascular incidents with increasing transportation noise levels.
OBJECTIVE: We present a narrative review of the evidence from epidemiologic studies and translation studies on the adverse cardiovascular effects of transportation noise.
METHODS: We describe the results of a recent Umbrella+ review that combines the evidence used in the 2018 WHO Environmental Noise Guidelines with more recent (post-2015) high-quality systematic reviews of original studies. High-quality systematic reviews were included based on the quality of literature search, risk of bias assessment, and meta-analysis methodology using AMSTAR 2.
RESULTS: Epidemiologic studies show that exposure to high levels of road traffic noise for several years lead to numerous adverse health outcomes, including premature deaths, ischemic heart disease (IHD), chronic sleep disturbances, and increased annoyance. Mechanistically, noise exposure triggers oxidative stress, inflammation, endothelial dysfunction, and circadian rhythm disruptions. These processes involve the activation of NADPH oxidase, mitochondrial dysfunction, and nitric oxide synthase uncoupling, leading to vascular and cardiac damage. Studies indicate that chronic noise exposure does not result in habituation, and susceptible individuals, such as those with pre-existing CVD, are particularly vulnerable.

Keywords: Epidemiology; Exposure assessment; Health studies; Human well-being; Meta-analysis; Noise pollution

Journal of Exposure Science & Environmental Epidemiology; https://doi.org/10.1038/s41370-024-00732-4

INTRODUCTION

Extensive research has established the adverse health impacts of environmental exposures contributing to the exposome, specifically air pollution, on cardiovascular disease (CVD), including conditions such as myocardial infarction (MI), heart failure, arrhythmia, hypertension, and stroke [1]. Recent studies have highlighted particulate matter with a diameter of ≤2.5 µm (PM2.5) as a major air pollutant, contributing to ~7.9 million annual deaths [2]. Various studies have observed that proximity to major roads increased cardiovascular health problems such as ischemic heart disease (IHD) or hypertension [3, 4]. These studies cannot clarify whether the observed adverse effects are from air pollution or from noise.

Surprisingly, much less attention has been given to transportation noise despite urban and suburban areas experiencing high levels of both air pollution and noise. Noise, defined as "unwanted and/or harmful sound," comes from transportation, occupational, leisure, residential, and industrial sources. With the present brief review, we want to focus on cardiovascular and metabolic health effects of transportation noise.

TRAFFIC NOISE EXPOSURE AND THE BURDEN OF DISEASE

In 2020, the European Environment Agency (EEA) reported that many people remain exposed to high road traffic noise levels, estimating that at least 20% of the EU population lives in areas where transportation noise exceeds 55 dB L_{den} (reviewed in refs. [5, 6]). The World Health Organization (WHO) indicates adverse health impacts are likely at these noise levels, particularly at night when noise should not exceed 45 dB(A) (Table 1). The U.S. Department of Transportation estimated that in 2018 7.3% of the U.S. population was exposed to road traffic noise levels above 50 dB $L_{aeq,24}$ (corresponding to a L_{den} of ≈53 dB), a number that the authors of the present review and even the U.S. Department of Transportation consider an underestimation of the real exposure levels of the U.S. population. In the EU, environmental noise, mainly from road transportation, is estimated to cause 12,000 premature deaths, 48,000 new cases of IHD, 6.5 million people experiencing chronic sleep disturbances, and 22 million individuals enduring significant annoyance annually. In 2020, it was estimated that 7.8 million, 5.2 million, and 7.9 million people in the U.S. were highly annoyed by aircraft, road, and rail traffic,

[1]Department of Cardiology, Cardiology I, University Medical Center of the Johannes Gutenberg-University, Mainz, Germany. [2]German Center for Cardiovascular Research (DZHK), Partnersite Rhine-Main, Mainz, Germany. [3]Center for Thrombosis and Hemostasis, University Medical Center of the Johannes Gutenberg-University, Mainz, Germany. [4]Department Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Allschwil, Switzerland. [5]University of Basel, Basel, Switzerland. [6]Quiet Communities Inc., Concord, MA, USA. ✉email: tmuenzel@uni-mainz.de

Received: 27 August 2024 Revised: 1 November 2024 Accepted: 4 November 2024
Published online: 10 December 2024

Table 1. WHO recommended limits for noise exposure levels and national legal thresholds for average noise exposure (https://www.euro.who.int/__data/assets/pdf_file/0009/383922/noise-guidelines-exec-sum-eng.pdf)[a].

Noise source	L_{den}	L_{night}	Quality of evidence	EU/US threshold
Road noise	<53 dB	<45 dB	strong	No legally binding limits for ambient noise. Legal limits for $L_{REL,8h}$ of 85–90 dB (US) and L_{EX} of 80–85 dB (EU) for occupational noise sources; peak (impulse) noise limits 135–140 dB.
Railway noise	<54 dB	<44 dB	strong	
Aircraft noise	<45 dB	<40 dB	strong	
Wind turbines	<45 dB	–	limited	
Leisure ambient noise	<70 dB (L_{Aeq},24 h)	–	limited	

[a]dB, decibel; L_{den}, average sound pressure level over 24 h adjusted for day-evening-night with a penalty of 5 dB for the evening time (7–11 pm or 6–10 pm) and a penalty of 10 dB for the night time (11pm–7am or 10pm–6am); L_{night}, average sound pressure level for night time (11pm–7am or 10pm–6am); L_{Aeq}, average sound pressure level over 24 h (A-weighted means adjusted for the human acoustic range). The recommended limits are related to the most seriously exposed face of the building. Strong quality of evidence requires fast action of policy makers, whereas limited quality of evidence requires substantial discussions among the decision makers, also considering the opinion of scientists, clinicians and health care system representatives. $L_{REL,8h}$, recommended exposure level over 8 h at workplace by the US CDC-associated National Institute for Occupational Safety and Health (NIOSH). L_{EX}, recommended exposure level over 24 h or 7 d at workplace by the European agency for occupational safety and health (EU-OSHA). Reused with permission [46].

respectively [7]. Urban expansion and increasing mobility demand are expected to raise the number of individuals exposed to road and railway noise by 2030, while aircraft noise exposure remains unchanged.

TRANSPORTATION NOISE AND CARDIOVASCULAR DISEASE AND DEATH

Recent evidence highlights the impact of environmental noise on cardiovascular health [5, 6]. The WHO Environmental Noise Guidelines for the European Region (WHO ENG) included studies up to 2015 [8]. A recent Umbrella+ review identified subsequent studies, combining the newest high-quality systematic reviews with original studies post-2015 [9]. High-quality systematic reviews were included based on the quality of literature search, risk of bias assessment, and meta-analysis methodology using AMSTAR 2 [10]. Eligible original studies were required to use reliable noise exposure assessment methods and account for relevant confounders. For mortality and incident CVDs, only cohort studies were included, whereas prevalent hypertension studies also considered case-control and cross-sectional studies if they were population-based, large, and methodologically sound [9].

Cardiovascular mortality

The Umbrella+ review identified 61 cardiovascular (ICD-10: I00-I99) and IHD (I20-I25) mortality papers, out of which 12 prospective cohort studies on road, railway, and/or aircraft noise were eligible for meta-analysis. The pooled effect estimate for cardiovascular mortality per 10 dB(A) of road traffic noise was 1.05 (95% CI: 1.02–1.07) [5] based on nine studies (1.05 (95% CI: 1.03–1.08) for ischemic heart disease mortality). Only two studies each were available for railway and aircraft noise, both finding minimal effects on cardiovascular mortality. Figure 1 shows the meta-analysis results. A Swiss case-crossover study found that short-term exposure to aircraft noise was associated with CVD mortality, particularly exposure to nighttime aircraft noise of 40–50 dB(A) and >50 dB(A) within two hours prior to a CVD death [11].

Ischemic heart disease (IHD)

The WHO ENG review found a relative risk (RR) of 1.08 (95% CI: 1.01–1.15) per 10 dB increase in L_{den} for IHD incidence due to road traffic noise [8, 12]. Recent studies, including a pooled Danish and Swedish cohort analysis [13] and a nationwide study from Denmark with over 2.5 million participants [14], reported hazard ratios (HRs) of 1.03 (95% CI: 1.00–1.05) and 1.05 (95% CI: 1.04–1.06) for road traffic noise. A meta-analysis combining WHO ENG [8, 12] with new studies found an RR of 1.04 (95% CI: 1.02–1.06) per 10 dB(A) increase in road traffic noise for IHD incidence [9].

Stroke

The WHO ENG included one cohort study on road traffic noise and incident stroke, finding an HR of 1.14 (95% CI: 1.03–1.25) [8]. Nine subsequent studies mostly indicated positive associations with road traffic noise, with risks near unity for rail and aircraft noise. A pooled Danish and Swedish cohort analysis found an HR of 1.06 (95% CI: 1.03–1.08) per 10 dB(A) increase in road traffic noise [15]. The Umbrella+ review reported an RR of 1.05 (95% CI: 1.01–1.08) per 10 dB(A) increase in road traffic noise for incident stroke [9].

Heart failure

The WHO ENG [8] did not address the effects of noise on heart failure. A 2023 meta-analysis found road traffic noise was associated with a 5% higher risk of heart failure per 10 dB(A) [16]. An updated meta-analysis found an RR of 1.04 (95% CI: 1.02–1.07) per 10 dB(A) increase in road traffic noise for heart failure [9].

Arrhythmia and/or atrial fibrillation

Few reviews and cohort studies exist on noise and arrhythmia and/or atrial fibrillation. A Danish nationwide cohort study with over 3.5 million participants reported weak associations between atrial fibrillation and road, railway, and aircraft noise [17]. An updated meta-analysis found an RR of 1.01 (95% CI: 1.00–1.01) per 10 dB(A) increase in road traffic noise [9]. After the publication of the Umbrella review, a pooled analysis of eleven prospective Nordic cohorts found a RR of 1.02 (95% CI: 1.00–1.04) per 10-dB of 5-year mean time-weighted exposure, which changed to 1.03 (1.01–1.06) when implementing a 53-dB cut-off [18]. It should be mentioned that we did not identify literature on associations of transportation noise with sudden death, out-of-hospital cardiac arrest, or ventricular arrhythmias.

Conclusions

The Umbrella+ review confirms associations between road traffic noise and various CVD diagnosis groups. Combining pooled effect estimates of IHD, stroke, hypertension, arrhythmia and heart failure results in a global CV risk increase of 3.2% (95% CI: 1.1–5.2%) per 10 dB higher road traffic noise (L_{den}) [9]. Evidence is less pronounced for railway and aircraft noise, as road traffic noise is more prevalent, many people exposed to moderate levels of railway and aircraft noise may not hear it because the road traffic noise is substantially higher. As a consequence, road traffic noise is

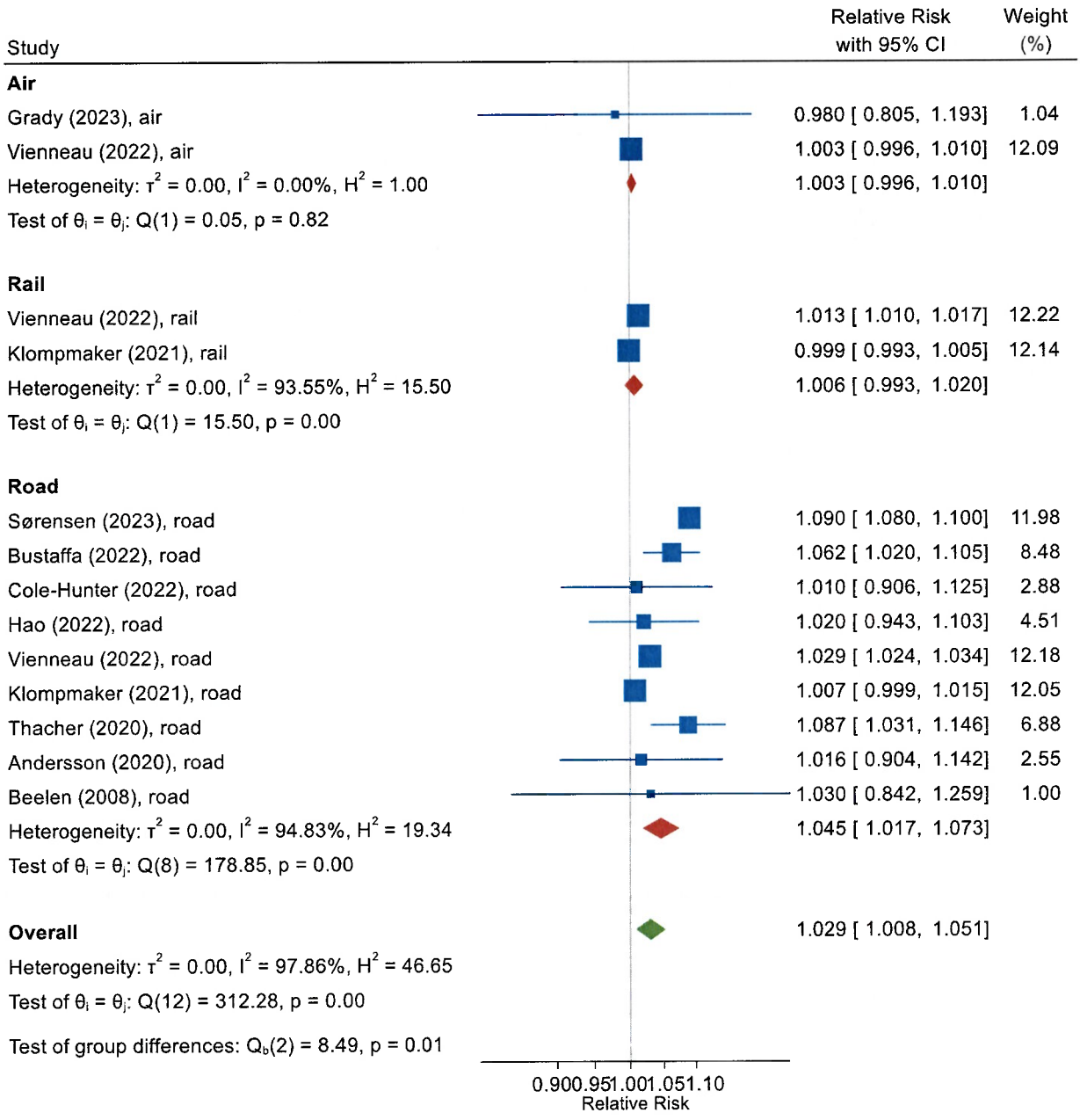


Fig. 1 Meta-analysis of cohort studies on cardiovascular mortality in relation to transportation noise, stratified by source. Relative risks refer to a 10 dB increase in L_{den}. Adapted with permission from [9].

potentially masking the effects of railway and aircraft noise in source-specific analysis. Intervention studies are needed to demonstrate risk reduction after noise mitigation. It would be also important to design studies to include measures of traffic related pollutants (NO_2 and PM2.5) and proximity of residence to roadway as complements to noise.

LOWER EFFECT THRESHOLD OF NOISE

The lower effect threshold of noise, below which no health effects are expected, is undetermined and likely varies by noise source and the different characteristics of noise (e.g., tonality, frequency). Different noise recommendations exist worldwide, with the EU using a 55 dB L_{den} threshold [8, 12] and the WHO recommending 53 dB(A) for road traffic noise [19]. Recent large cohort studies suggest effects starting around 45 dB L_{den} for various cardiovascular diagnoses and diabetes [9].

TRANSPORTATION NOISE AND DIABETES AND OBESITY

Recent cohort studies have linked transportation noise, especially from road traffic, with a higher risk of diabetes (reviewed in ref. [5]). A meta-analysis found that a 10 dB(A) increase in road traffic noise was associated with a relative risk (RR) for diabetes of 1.06 (95% CI: 1.03–1.09). Studies have suggested that noise may affect sleep quality and contribute to metabolic changes leading to diabetes.

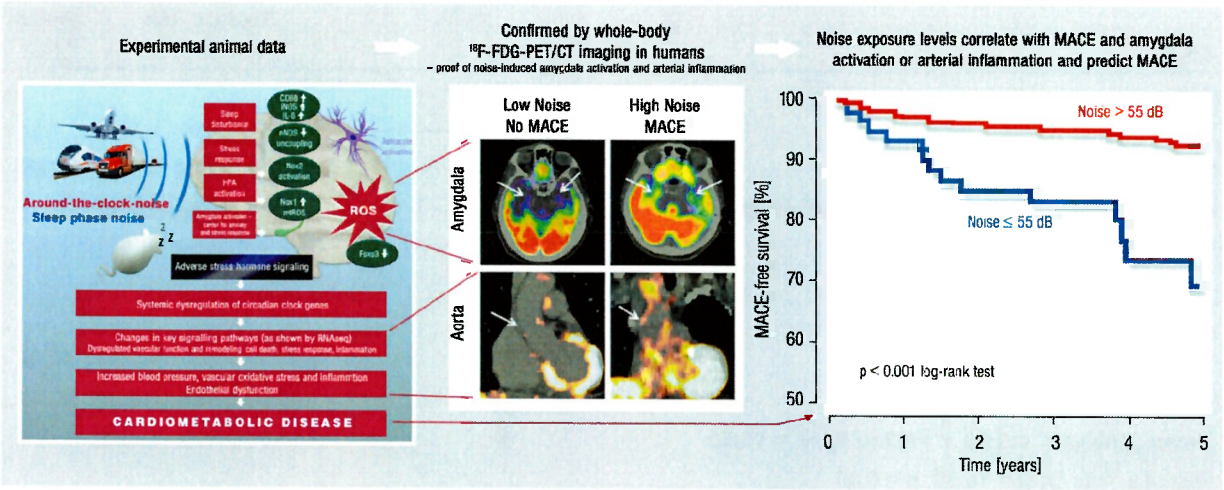


Fig. 2 Key data on health effects of noise through the brain-heart/vessel-axis. *Left panel:* Main results of animal studies regarding brain-heart/vessel interaction. *Middle and right panel:* Proof-of-concept translational study in humans demonstrating the association between transport (road and aircraft) noise-induced cerebral (amygdala relative to cortical) metabolic activity and arterial inflammation increasing major adverse cardiovascular events (MACE) [29, 30]. Reused with permission from ref. [30].

Research also indicates that noise exposure may contribute to obesity (reviewed in ref. [5]). Several studies found associations between road traffic noise and increased measures of adiposity, suggesting that noise can affect weight gain throughout life.

NOISE AND EPIGENETIC CHANGES: ADVERSE IMPACTS ON THE IMMUNE SYSTEM AND VASCULAR FUNCTION

Cross-sectional cohort studies have found that exposure to transportation noise can have an impact on the immune system. Two studies observed that noise increases levels of IL-12 and high-sensitivity CRP (C-reactive protein) while decreasing natural killer cell populations and activity, although the extent of noise effects on the immune system is not consistently uniform across all studies [20–22]. Furthermore, alterations in the immune system have been linked to elevated circulating cortisol levels and heightened noise sensitivity [21, 22]. Higher cortisol levels may also be related to nocturnal noise exposure and impaired circadian rhythm [23, 24].

Interestingly, a study based on the Swiss SAPALDIA cohort 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 (e.g., CRP), cellular development, and immune responses [25]. Findings in the same cohort suggested that chronic exposure to nocturnal intermittent train or road traffic noise increases arterial stiffness (reflecting endothelial dysfunction), as determined by pulse wave velocity [26]. This finding is supported by a German cohort study, showing that long-term exposure to nighttime road traffic noise is associated with subclinical atherosclerosis, especially in participants with early arterial calcification [27, 28].

In summary, these findings offer pathophysiological and molecular evidence from human studies, highlighting the effects of transportation noise on incident CVD. Notably, the results from these human studies, including stress pathways, inflammation, oxidative stress, arterial stiffness, and endothelial/cardiac dysfunction, align with mechanistic data from animal studies (reviewed in refs. [5, 6]).

NOISE ANNOYANCE

Noise annoyance, a psychological response to unwanted sounds, can be an early indicator of more severe health risks. It involves cognitive, emotional, and behavioral reactions influenced by personal, social, and situational factors. Recent studies have shown that transportation noise, particularly from roads and aircraft, is associated with increased annoyance levels, contributing to stress and negatively impacting cardiovascular health (reviewed in refs. [5, 6]). Annoyance from noise can lead to increased stress hormone levels and inflammation, further contributing to cardiovascular risk.

NOISE AND AMYGDALAR ACTIVATION

The link between noise exposure and major adverse cardiovascular events (MACE) was observed in a 2020 study where stress-associated neural activity was associated with arterial inflammation in 498 healthy subjects without active cancer or CVD [29]. The neural activity was determined as the ratio of amygdala to regulatory cortical metabolic activity envisaged by the ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (PET–CT) imaging. At the same time, aortic inflammation was also determined using PET-CT to observe ^{18}F-fluorodeoxyglucose uptake. The results indicated that the increased noise exposure level at the individual's home address was linked to elevated amygdala activity, arterial inflammation, and higher risk of MACE, independently of confounders such as air pollution, socioeconomic status, and other established CVD risk factors. The study's authors conclude that the association between higher noise exposure and MACE occurred via elevated amygdala activity and arterial inflammation (Fig. 2) [29, 30]. Interestingly, a similar pathway was previously observed to be responsible for the association between perceived stress and socioeconomic disparities (e.g., lower education or income) and CVD [31].

MECHANISTIC INSIGHTS: TRANSLATIONAL STUDIES IN HUMANS AND ANIMALS

Oxidative stress and endothelial dysfunction

Translational studies in humans with and without CVD have demonstrated that exposure to transportation noise for one night (47 dB(A) L_{eq}) leads to a significant increase in oxidative stress markers such as 3-nitrotyrosine and 8-isoprostane in serum and a significant degree of endothelial dysfunction as indicated by a reduction of flow-mediated dilation (FMD) (Fig. 3) (reviewed in refs. [5, 6]). Importantly, the deterioration of FMD was stronger in

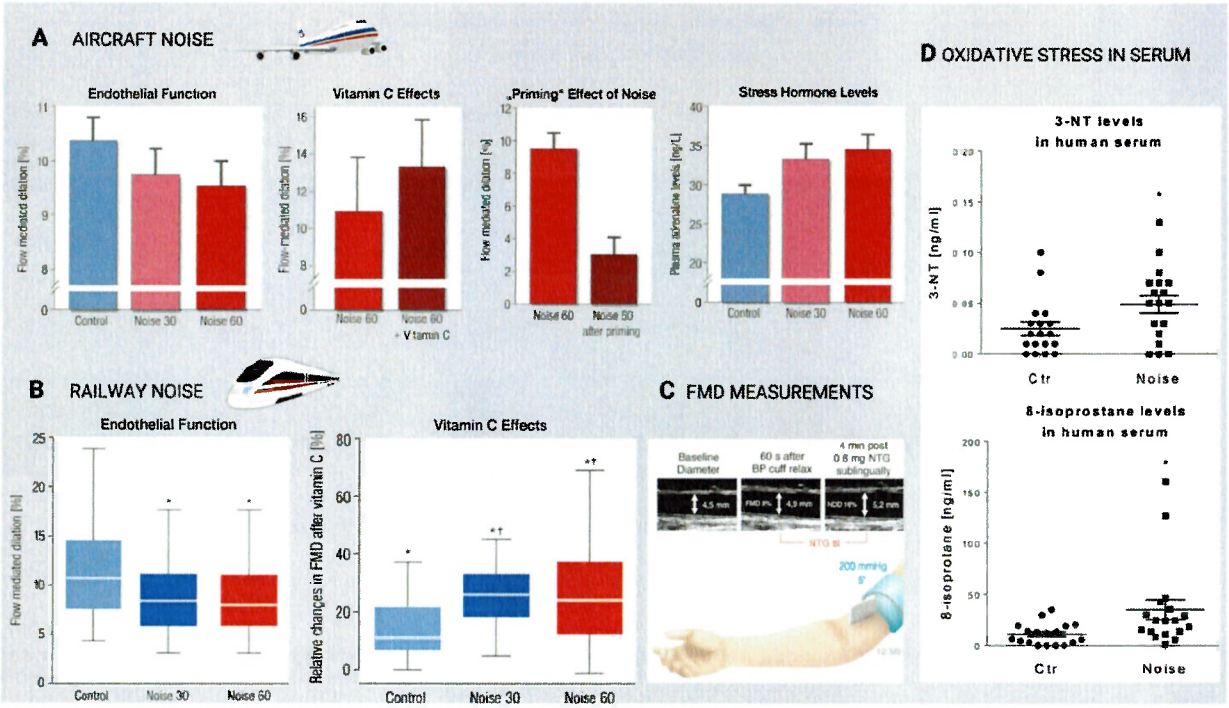


Fig. 3 Key effects of noise observed in human field studies. A Effects of 30 and 60 aircraft noise events on the brachial artery (Noise30 and Noise60) of 70 healthy subjects. Vitamin C effects were assessed in a subgroup of the cohort. A priming effect of aircraft noise on endothelial function was observed, i.e., previous exposure to Noise30 caused Noise60 to have a significantly stronger reduction of flow-mediated dilation [52]. 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. **C** Methodology of FMD. **D** Effects of aircraft noise on oxidative stress markers (3-nitrotyrosine [3-NT] and 8-isoprostane) in serum that were measured in the samples of the aircraft noise study and published in ref. [32]. Adapted from [32] with permission. Copyright ©2018, Oxford University Press.

subjects with already established CVD. The acute administration of the antioxidant vitamin C has been shown to improve endothelial function, indicating the roll of oxidative stress in noise-induced vascular damage.

Preclinical studies revealed that oxidative stress in noise-exposed mice (72 dB(A) L_{eq}, around-the-clock for 4 days) is primarily driven by the activation of NADPH oxidase (NOX-2), a key enzyme in inflammatory cells like leukocytes and macrophages that produces reactive oxygen species (ROS) but is also driven by a dysfunctional, uncoupled endothelial nitric oxide synthase [32]. Noise exposure also activates inflammatory pathways. It triggers the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, leading to the release of stress hormones like cortisol and catecholamines (Fig. 4) (reviewed in refs. [5, 6]). These hormones induce a pro-inflammatory state characterized by elevated levels of interleukins (IL-6, IL-1β) and proinflammatory monocytes. This inflammation can lead to vascular changes that contribute to the progression of atherosclerosis and other cardiovascular conditions.

Recently we also demonstrated that noise exposure can dysregulate gene networks within the vasculature. This includes the upregulation of genes involved in TGF-beta signaling, autophagy, and growth regulation and downregulation of genes associated with cell cycle control and apoptosis [33]. These changes in gene expression further impair endothelial and vascular signaling, contributing to cardiovascular dysfunction.

An additional finding from our preclinical studies is that nighttime noise exposure has a more detrimental effect than daytime noise. We demonstrated that nighttime noise, as opposed to daytime noise, led to significantly higher blood pressure, a greater increase in neurohormonal release, elevated oxidative stress in vascular tissue, increased endothelin-1 expression within the vasculature and interestingly no endothelial dysfunction at all. These factors may explain, at least in part, why nighttime noise contributes to greater vascular stiffness and higher blood pressure compared to daytime noise (for review, see [34]). Moreover, we observed circadian clock dysregulation, primarily involving the downregulation of FOXO3, a transcription factor serving as a central signaling hub. We tested the effect of bepridil, a FOXO3 activator, calcium antagonist, anti-anginal, and class IV anti-arrhythmic drug. Bepridil prevented noise-induced endothelial dysfunction, increased FOXO3 mRNA expression, and reduced vascular and cerebral oxidative stress [32]. Based on these findings, we hypothesized that the adverse effects of nighttime noise are partly due to circadian rhythm disruption, as noise during sleep causes sleep fragmentation and reduced sleep quality, thereby amplifying stress responses leading to more pronounced oxidative stress and endothelial dysfunction [32–34]

This disruption affects central and peripheral circadian clocks, contributing to metabolic and cardiovascular dysfunction. Nighttime noise exposure causes also a significant downregulation and uncoupling of neuronal nitric oxide synthase (nNOS), leading to a neuroinflammatory phenotype [32] that probably affects cognitive functions and increases cardiovascular risk.

Noise exposure affects the neuroendocrine system by elevating levels of angiotensin II and endothelin-1, hormones that regulate blood pressure and fluid balance (Fig. 4). This elevation increases oxidative stress and inflammation in the brain's microvasculature and conductance vessels, contributing to hypertension and other cardiovascular issues (reviewed in refs. [5, 6]). The sympathetic nervous system activation due to oxidative stress further releases catecholamines, which can exacerbate cardiovascular damage. The following sections briefly explain how stress hormone-mediated receptor signaling can activate sources of ROS

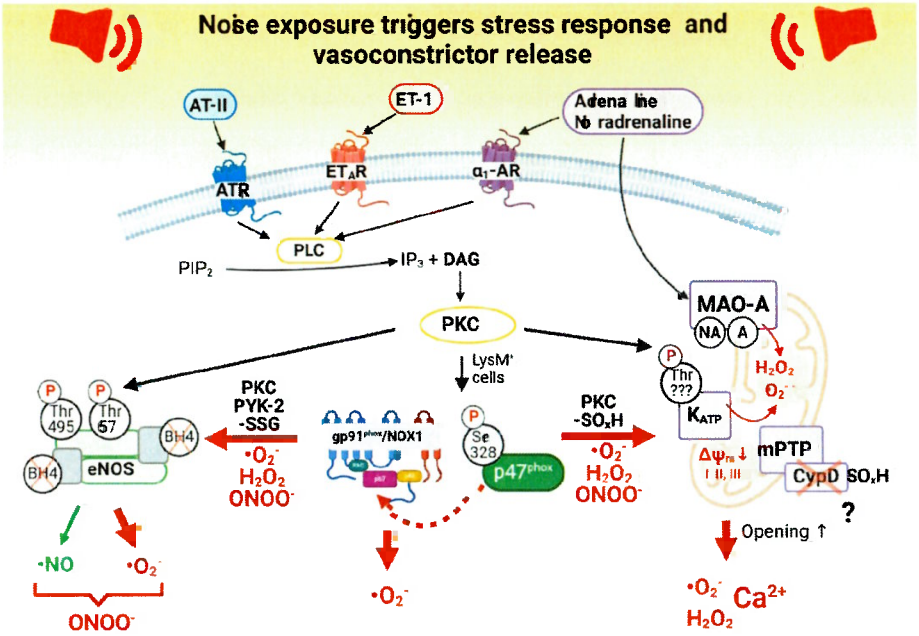


Fig. 4 Oxidative stress pathways activated by noise. Noise causes stress hormone release (catecholamines and cortisol) and downstream endocrinal activation of vasoconstrictors activating common disease pathways, such as oxidative stress. Angiotensin II (AT-II) and endothelin-1 (ET-1) lead to the formation of diacylglycerol (DAG) from phosphatidylinositol 4,5-bisphosphate (PIP_2), a potent activator of protein kinase C (PKC), via their receptors and the activation of phospholipase C (PLC). (1) PKC via phosphorylation of $p47^{phox}$ at serine 328 causes activation of the phagocytic NADPH oxidase (NOX-2) and potentially NOX-1. The expression of NOX-2 is upregulated by noise-triggered immune cell infiltration (lysozyme M-positive ($LysM^+$) cells) and systemic inflammatory conditions. NOX-2 (and NOX-1, especially in the brain) produces superoxide ($O_2^{\bullet-}$) and via dismutation also hydrogen peroxide (H_2O_2). NOX-4 was not changed by noise and NOX-5 (relevant for humans) was not studied so far. (2) Dysfunction of endothelial nitric oxide synthase (eNOS) is mediated by noise-dependent activation of PKC and phosphorylation of threonine 495. Alternatively, NOX-2-dependent ROS formation may activate PKC [53] and protein tyrosine kinase 2 (PYK-2) [54, 55], causing adverse phosphorylation at tyrosine 657 and threonine 495. Uncoupling of eNOS may be induced by noise-driven oxidative depletion of tetrahydrobiopterin (BH_4) and S-glutathionylation (-SSG) of eNOS by ROS originating from NOX-2 [56]. Semi-uncoupled eNOS may represent a potent source of peroxynitrite. (3) Noise also leads to mitochondrial ROS formation, generating both $O_2^{\bullet-}$ and H_2O_2. Noradrenaline (NA) and adrenaline (A) originating from sympathetic activation are substrates of monoamine oxidases (MAO) that produce H_2O_2. NA and A can also activate PKC through adrenergic receptor (α_1-AR). PKC seems to activate the mitochondrial K_{ATP} channel by phosphorylation of a threonine residue with subsequent depolarization of the mitochondrial membrane ($\Delta\Psi_m\downarrow$) and $O_2^{\bullet-}$ formation from respiratory complexes I, II and III. Mitochondrial H_2O_2 / $O_2^{\bullet-}$ and calcium are released to the cytosol upon the mitochondrial permeability transition pore (mPTP) opening (e.g., by thiol oxidation of the regulatory subunit cyclophilin D (CypD) [57]). K_{ATP} channel activation and mPTP opening can also be stimulated by redox-crosstalk with H_2O_2 (probably also $O_2^{\bullet-}$ via peroxynitrite) derived from NOX-2 [58]. So far, there is no evidence for the role of xanthine oxidase in noise's non-auditory (indirect) effects. This scheme was adapted from [35] with permission and created using biorender.com.

(superoxide, $O_2^{\bullet-}$ and hydrogen peroxide, H_2O_2) and lead to oxidative stress conditions (reviewed in ref. [35]).

NADPH oxidases

NOX-2 (gp91phox), the phagocyte isoform of NADPH oxidases, is a key enzyme in host defense. Whereas other NADPH oxidase isoforms (e.g., NOX-1, NOX-4, NOX-3, and DUOX-2) play a role in noise-induced hearing loss, the role of NADPH oxidases in the non-auditory (indirect) pathology is less explored. Upon noise exposure, NOX-2 protein and NOX-2 mRNA levels are consistently upregulated in the murine aorta and heart [32, 33]. Also, a more pronounced activation state of NOX-2 was reported for noise-exposed mice, which was driven by angiotensin-II or endothelin-1 dependent diacylglycerol-mediated protein kinase C (PKC) activation with subsequent Ser328 phosphorylation of p47phox, the cytosolic regulator, and activation of NOX-2 (Fig. 4). Evidence of oxidative stress is readily detectable in the aorta, heart, and brains of mice exposed to noise [32, 33] and the serum of noise-exposed healthy subjects. Importantly, mice with a genetic deletion of NOX-2 gene or ablation of inflammatory monocytes ($LysM^+$ cells) are protected from this oxidative stress and the subsequent endothelial dysfunction [32, 36]. Further support for a central role of NOX-2 in noise-mediated pathophysiology comes from studies showing an additive upregulation of NOX-2 protein in noise-exposed hypertensive and MI mice (reviewed in ref. [5]).

Mitochondria

Mitochondria are well-known producers of ROS and are known to contribute to oxidative damage in IHD and hypertension (reviewed in ref. [35]). Different noise sources and patterns were reported to cause mitochondrial damage in the form of cardiac fibrosis, enlarged cardiac mitochondria, swelling, matrix dilution, cristolysis, DNA damage and reduced connexin 43 contents (reviewed in ref. [5]. These observations can be linked to high noradrenaline levels, monoamine oxidase (MAO) activity, disturbed mitophagy, potentially negatively impacting permeability transition (e.g., mPTP), and calcium handling. Catecholamines (or serotonin) serve as MAO substrates enabling significant ROS formation. Accordingly, an additive increase in mitochondrial superoxide levels was seen in the hearts of noise-exposed mice with MI in conjunction with impaired mitochondrial respiration and oxygen handling [37]. Pathways that could be involved in noise-dependent mitochondrial ROS formation are shown in Fig. 4.

Uncoupled nitric oxide synthases

Due to the excessive superoxide formation in noise-exposed animals, endothelial NOS (eNOS) in the aorta (and neuronal - nNOS in the brain) uncouples, which means that it transforms into a source of $O_2^{\bullet-}$ and H_2O_2 instead of proper synthesis of nitric oxide ($^{\bullet}NO$). NOS uncoupling was previously demonstrated in tissues of noise-exposed mice by dihydroethidium staining in the presence of the eNOS inhibitor N^G-nitro-L-arginine methyl ester (L-NAME) [32, 33]. eNOS is redox-sensitive because of its reliance on a readily oxidizable cofactor, tetrahydrobiopterin (BH_4). Without BH_4, eNOS cannot produce $^{\bullet}NO$, but instead produces $O_2^{\bullet-}$. The concomitant formation of $^{\bullet}NO$ and $O_2^{\bullet-}$ by uncoupled eNOS generates peroxynitrite, which in term reacts with proteins to result in their tyrosine nitration as observed in noise-exposed mice and humans [32, 33]. eNOS uncoupling diminishes $^{\bullet}NO$ bioavailability in the aortas of noise-exposed mice as determined by the direct quantification of $^{\bullet}NO$ using electron spin resonance spectroscopy. Adverse dysregulated phosphorylation by excessive ROS could further aggravate eNOS dysfunction. Another redox-dependent uncoupling mechanism is eNOS S-glutathionylation, which was also increased in the aorta and heart of noise-exposed mice [32, 33]. The latter effect was not observed in NOX-2–deficient mice and was aggravated in noise-exposed hypertensive mouse hearts. The noise-triggered adverse regulation of eNOS that switches the enzyme to a peroxynitrite and superoxide source is shown in Fig. 4.

LACK OF TOLERANCE DEVELOPMENT TO CARDIOVASCULAR HEALTH EFFECTS OF NOISE

Chronic exposure of mice to aircraft noise for 4 weeks does not result in habituation concerning the cardiovascular side effects. Persistent endothelial dysfunction and elevated blood pressure were observed in studies exposing animals to noise for up to 28 days [38]. The formation of ROS increased over time, particularly in the aorta, heart, and brain. This oxidative stress was marked by a peak oxidative burst in whole blood after 4–7 days. Additionally, increased superoxide in the brain was associated with the downregulation of neuronal nitric oxide synthase (NOS3) and FOXO3 genes. Inflammatory markers like VCAM-1 mRNA were consistently upregulated, indicating that mice did not acclimate to chronic noise stress, and endothelial dysfunction and inflammation persisted throughout the exposure period.

NOISE PRECONDITIONING AND MYOCARDIAL INFARCTION

The impact of noise on susceptible patients, such as those with acute coronary syndromes [39], was also studied on a mechanistic basis by exposing mice to 72 dB(A) noise levels with peaks at 85 dB(A) for up to 4 days [37]. This exposure activated pro-inflammatory gene expression related to myeloid cell adhesion and diapedesis pathways. Noise exposure led to increased adhesion and infiltration of inflammatory myeloid cells in vascular and cardiac tissues, and a higher percentage of leukocytes showed a pro-inflammatory phenotype characterized by ROS and upregulation of NOX-2 and NF-κB phosphorylation. This resulted in "priming" of the heart for ischemic damage. Subsequent MI caused more pronounced endothelial dysfunction and elevated vascular ROS levels in noise-preconditioned animals (reviewed in ref. [5]).

Translational studies in the Gutenberg Health Study Cohort found that individuals with prior noise exposure and annoyance had elevated baseline CRP levels and a more significant decline in left ventricular ejection fraction after an MI [37]. People with acute coronary syndromes were particularly susceptible to aircraft noise, with a hazard ratio (HR) of 1.24 (95%-CI: 0.97–1.58) per 10 dB increase in L_{den} aircraft noise [39]. Combined analysis showed an HR of 1.31 (95%-CI: 1.03–1.66) for recurrence of cardiovascular events and all-cause mortality, indicating high susceptibility of CVD patients to noise.

RECOVERY TIME FOR CARDIOVASCULAR SYSTEM AFTER NOISE STRESS

Recovery from noise-induced endothelial dysfunction in the aorta was possible within 1–4 days of noise cessation in mice [40]. Acetylcholine-dependent relaxation measurements confirmed this recovery. Partial correction of vascular oxidative stress and blood pressure and normalization of inflammatory markers such as VCAM-1 and IL-6 were observed. However, endothelial dysfunction and inflammation in cerebral microvessels did not improve, suggesting that microcirculation requires longer recovery to reverse noise-induced vascular dysfunction (reviewed in ref. [5]).

MODIFYING NOISE-INDUCED HEALTH EFFECTS THROUGH α1AMPK ACTIVATION

Non-pharmacological approaches like physical activity, a balanced diet, and weight management are effective in preventing and treating CVD and diabetes [41]. It is known that exercise can mitigate the impact of air pollution-induced CVD and mortality. Activation of α1AMPK through exercise, intermittent fasting, and pharmacological methods (e.g., AICAR) was explored in mice exposed to aircraft noise [42]. Noise exposure-impaired endothelial function in the aorta, mesenteric arteries, and retinal arterioles was accompanied by increased vascular oxidative stress and asymmetric dimethylarginine formation. α1AMPK activation effectively prevented endothelial dysfunction and oxidative stress, supported by RNA sequencing data. Absence of endothelium-specific α1AMPK worsened noise-induced vascular damage, nullifying the protective effects of exercise or fasting, highlighting the importance of α1AMPK activation in mitigating noise-induced cardiovascular damage (reviewed in ref. [5]).

PREVENTION AND MITIGATION STRATEGIES TO REDUCE TRANSPORTATION NOISE

Transportation noise is a public health problem affecting large swaths of the global population. The onus is on policymakers and other decision makers to take action to protect the public from the harms of environmental noise. Particular attention should be paid to populations exposed to the highest levels of noise which, at least in the United States, tend to affect low income communities disproportionately [43, 44], as well as other vulnerable populations, such as those with pre-existing CVD. Professional societies, e.g., American Heart Association, American College of Cardiology, European Society of Cardiology, should incorporate environmental noise into CVD prevention guidelines and educational materials. Policymakers should incorporate environmental noise criteria into program and policy screening tools and enact measures to mitigate existing sources of harmful environmental noise. The US EPA has provided a cumulative risk assessment framework that could accommodate noise (https://www.epa.gov/risk/framework-cumulative-riskassessment). By applying the cumulative risk framework provided by the US EPA (Environmental Protection Agency) [45], a more holistic approach to policy development and mitigation is potentially achieved.

The mitigation measures proposed below were reviewed extensively in refs. [5, 46]. Local authorities can employ several strategies to mitigate road, railways, and aircraft noise as outlined in a policy brief of the European Commission [47]. Priority measures are at the source. Special noise-reducing asphalt can decrease noise by 3 to 6 dB(A). Reducing speed limits can decrease noise by ~1 dB(A) per 10 km/h reduction. Low speed (20 miles per hour) in combination with electrification of cars,

reduces noise in urban areas to a large extent. At higher speed, electrification is less effective as the sound generated by the interaction of tires and pavement is the dominating noise source. Promoting the use of low-noise tires can potentially reduce noise by 2–3 dB(A). Investing in urban infrastructure such as bike lanes, ride-sharing programs, and public transportation can also help to reduce urban noise levels as well as air pollution levels. As an ultimate measure, sound proof windows reduce indoor noise substantially and for road and railway noise, erecting barriers along busy lines in densely populated areas can reduce noise levels by up to 10 dB(A).

To address aircraft noise, implementing GPS-guided routes can help avoid densely populated areas, thus reducing noise impact. Prohibiting take-offs and landings during nighttime hours can significantly reduce sleep disturbances. Continuous descent approaches with steeper descents, and lower throttle settings can minimize noise during landings. Furthermore, promoting the development and use of quieter aircraft technology can have a long-term impact on reducing noise pollution from aviation.

For railway noise, regular maintenance and grinding of tracks can help reduce noise generated by train operations. Replacing traditional cast-iron block brakes with composite materials can lower noise levels during braking. Prohibiting railway operations near residential areas during nighttime can help reduce disturbances. Investing in vibration-damping track systems and sound barriers along railway lines can also mitigate noise pollution from trains.

By combining these strategies, authorities can substantially reduce noise, particularly in densely populated areas. A comprehensive approach that includes technological advancements, infrastructure improvements, and policy changes will most effectively address transportation noise pollution and help to improve public health.

INTERACTION BETWEEN TRANSPORTATION NOISE AND AIR POLLUTION

Noise and air pollution often co-occur, having a common source in fossil fuel-powered vehicles, equipment, and machinery. Their combined exposure can adversely affect cardiovascular health, leading to cumulative risk increases in humans as reported for diabetes [48], stroke [49], and MI [50]. Animal studies using combined exposure systems revealed that both stressors independently cause endothelial dysfunction and oxidative stress, and their combination leads to more severe cardiovascular damage [51]. This interaction underscores the importance of considering multiple environmental factors in assessing cardiovascular risk.

CONCLUSIONS

Transportation noise significantly impacts cardiovascular health through mechanisms involving oxidative stress, inflammation, endothelial dysfunction, gene dysregulation, circadian rhythm disruption, metabolic changes, and psychological stress. Translational studies in humans and experimental animals have provided valuable insights into these processes, emphasizing the need for comprehensive strategies to mitigate noise pollution and its health impacts. Based on the existing evidence concerning noise, it's time now for immediate policy actions to decrease exposure to noise. While this is an action that is supported by the evidence, translation of science into policy and then the implementation of such policies through regulation, rules or guidance takes a long time. Thus we have to consider tactical approaches that can be implemented in the short-term together with health professionals, who can advise their patients to reduce exposure. Thus, we are recommending both a longer-term strategic approach as a solution and a shorter-term tactical approach.

Noise should be acknowledged as a significant cardiovascular risk factor along with other environmental hazards such as ambient air pollution and exposure to chemicals, e.g., in the CVD prevention guidelines of professional societies. Public officials and decision makers should act to reduce public exposure to harmful levels of noise and adhere to the national limits as well as WHO recommendations (Table 1). Further studies are needed to explore the interactions between noise and other environmental stressors and effective public protection interventions.

REFERENCES

1. Munzel T, Sorensen M, Hahad O, Nieuwenhuijsen M, Daiber A. The contribution of the exposome to the burden of cardiovascular disease. Nat Rev Cardiol. 2023;20:651–69.
2. Lelieveld J, Klingmuller K, Pozzer A, Poschl U, Fnais M, Daiber A, et al. Cardiovascular disease burden from ambient air pollution in Europe reassessed using novel hazard ratio functions. Eur Heart J. 2019;40:1590–6.
3. Brugge D, Lane K, Padro-Martinez LT, Stewart A, Hoesterey K, Weiss D, et al. Highway proximity associated with cardiovascular disease risk: the influence of individual-level confounders and exposure misclassification. Environ Health Glob Access Sci Source. 2013;12:84.
4. Hoffmann B, Moebus S, Stang A, Beck EM, Dragano N, Mohlenkamp S, et al. Residence close to high traffic and prevalence of coronary heart disease. Eur Heart J. 2006;27:2696–702.
5. Munzel T, Molitor M, Kuntic M, Hahad O, Roosli M, Engelmann N, et al. Transportation noise pollution and cardiovascular health. Circ Res. 2024;134:1113–35.
6. Munzel T, Sorensen M, Daiber A. Transportation noise pollution and cardiovascular disease. Nat Rev Cardiol. 2021;18:619–36.
7. Huang CH, Seto E. Estimates of population highly annoyed from transportation noise in the United States: an unfair share of the burden by race and ethnicity. Environ Impact Assess Rev. 2024;104:107338.
8. WHO. WHO environmental noise guidelines for the European Region. http://www.euro.who.int/en/publications/abstracts/environmental-noise-guidelines-for-the-european-region-2018. 2018.
9. Engelmann N, Blanes Guàrdia N, Fons Esteve J, Vienneau D, M. R Environmental noise health risk assessment: methodology for assessing health risks using data reported under the Environmental Noise Directive (Eionet Report – ETC HE 2023/X). *European Topic Centre on Human Health and the Environment*, 2023. https://www.eionet.europa.eu/etcs/etc-he/products/etc-he-products/etc-he-reports/etc-he-report-2023-11-environmental-noise-health-risk-assessment-methodology-for-assessing-health-risks-using-data-reported-under-the-environmental-noise-directive.
10. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.
11. Saucy A, Schaffer B, Tangermann L, Vienneau D, Wunderli JM, Roosli M. Does night-time aircraft noise trigger mortality? A case-crossover study on 24 886 cardiovascular deaths. Eur Heart J. 2021;42:835–43.
12. Kempen EV, Casas M, Pershagen G, Foraster M. 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. 2018;15:379.
13. Pyko A, Roswall N, Ögren M, Oudin A, Rosengren A, Eriksson C, et al. Long-term exposure to transportation noise and ischemic heart disease: a pooled analysis of nine Scandinavian cohorts. Environ Health Perspect. 2023;131:17003.
14. Thacher JD, Poulsen AH, Raaschou-Nielsen O, Hvidtfeldt UA, Brandt J, Christensen JH, et al. Exposure to transportation noise and risk for cardiovascular disease in a nationwide cohort study from Denmark. Environ Res. 2022;211:113106.
15. Roswall N, Pyko A, Ogren M, Oudin A, Rosengren A, Lager A, et al. Long-term exposure to transportation noise and risk of incident stroke: a pooled study of nine Scandinavian cohorts. Environ Health Perspect. 2021;129:107002.
16. Fu X, Wang L, Yuan L, Hu H, Li T, Zhang J, et al. Long-term exposure to traffic noise and risk of incident cardiovascular diseases: a systematic review and dose-response meta-analysis. J Urban Health. 2023;100:788–801.
17. Thacher JD, Poulsen AH, Hvidtfeldt UA, Raaschou-Nielsen O, Ketzel M, Jensen SS, et al. Long-term exposure to transportation noise and risk for atrial fibrillation: a Danish nationwide cohort study. Environ Res. 2022;207:112167.
18. Thacher JD, Roswall N, Ögren M, Pyko A, Åkesson A, Oudin A, et al. Residential exposure to transportation noise and risk of incident atrial fibrillation: a pooled study of 11 prospective Nordic cohorts. Lancet. 2024;46:101091
19. World Health Organization Environmental noise guidelines for the European region. WHO Regional Office for Europe, Copenhagen; 2018.

20. Thiesse L, Rudzik F, Kraemer JF, Spiegel K, Leproult R, Wessel N, et al. Transportation noise impairs cardiovascular function without altering sleep: the importance of autonomic arousals. Environ Res. 2020;182:109086.
21. Cai Y, Hansell AL, Blangiardo M, Burton PR, BioShaRe, de Hoogh K, et al. Long-term exposure to road traffic noise, ambient air pollution, and cardiovascular risk factors in the HUNT and lifelines cohorts. Eur Heart J. 2017;38:2290–6.
22. Kim A, Sung JH, Bang JH, Cho SW, Lee J, Sim CS. Effects of self-reported sensitivity and road-traffic noise levels on the immune system. PLoS ONE. 2017;12:e0187084.
23. Ising H, Ising M. Chronic cortisol increases in the first half of the night caused by road traffic noise. Noise Health. 2002;4:13–21.
24. Selander J, Bluhm G, Theorell T, Pershagen G, Babisch W, Seiffert I, et al. Saliva cortisol and exposure to aircraft noise in six European countries. Environ Health Perspect. 2009;117:1713–7.
25. Eze IC, Jeong A, Schaffner E, Rezwan FI, Ghantous A, Foraster M, et al. Genome-wide DNA methylation in peripheral blood and long-term exposure to source-specific transportation noise and air pollution: the SAPALDIA Study. Environ Health Perspect. 2020;128:67003.
26. Foraster M, Eze IC, Schaffner E, Vienneau D, Heritier H, Endes S, et al. Exposure to road, railway, and aircraft noise and arterial stiffness in the SAPALDIA study: annual average noise levels and temporal noise characteristics. Environ Health Perspect. 2017;125:097004.
27. Kalsch H, Hennig F, Moebus S, Mohlenkamp S, Dragano N, Jakobs H, et al. Are air pollution and traffic noise independently associated with atherosclerosis: the Heinz Nixdorf Recall Study. Eur Heart J. 2014;35:853–60.
28. Hennig F, Moebus S, Reinsch N, Budde T, Erbel R, Jockel KH, et al. Investigation of air pollution and noise on progression of thoracic aortic calcification: results of the Heinz Nixdorf Recall Study. Eur J Prev Cardiol. 2020;27:965–74.
29. Osborne MT, Radfar A, Hassan MZO, Abohashem S, Oberfeld B, Patrich T, et al. A neurobiological mechanism linking transportation noise to cardiovascular disease in humans. Eur Heart J. 2020;41:772–82.
30. Munzel T, Steven S, Hahad O, Daiber A. The sixth sense is involved in noise-induced stress responses and vascular inflammation: evidence for heightened amygdalar activity in response to transport noise in man. Eur Heart J. 2020;41:783–5.
31. Tawakol A, Ishai A, Takx RA, Figueroa AL, Ali A, Kaiser Y, et al. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. Lancet. 2017;389:834–45.
32. Kroller-Schon S, Daiber A, Steven S, Oelze M, Frenis K, Kalinovic S, et al. Crucial role for Nox2 and sleep deprivation in aircraft noise-induced vascular and cerebral oxidative stress, inflammation, and gene regulation. Eur Heart J. 2018;39:3528–39.
33. Munzel T, Daiber A, Steven S, Tran LP, Ullmann E, Kossmann S, et al. Effects of noise on vascular function, oxidative stress, and inflammation: mechanistic insight from studies in mice. Eur Heart J. 2017;38:2838–49.
34. Münzel T, Kröller-Schön S, Oelze M, Gori T, Schmidt FP, Steven S, et al. Adverse cardiovascular effects of traffic noise with a focus on nighttime noise and the New WHO Noise Guidelines. Annu Rev Public Health. 2020;41:309–28.
35. Sorensen M, Pershagen G, Thacher JD, Lanki T, Wicki B, Roosli M, et al. Health position paper and redox perspectives - Disease burden by transportation noise. Redox Biol. 2024;69:102995.
36. Frenis K, Helmstadter J, Ruan Y, Schramm E, Kalinovic S, Kroller-Schon S, et al. Ablation of lysozyme M-positive cells prevents aircraft noise-induced vascular damage without improving cerebral side effects. Basic Res Cardiol. 2021;116:31.
37. Molitor M, Bayo-Jimenez MT, Hahad O, Witzler C, Finger S, Garlapati VS, et al. Aircraft noise exposure induces pro-inflammatory vascular conditioning and amplifies vascular dysfunction and impairment of cardiac function after myocardial infarction. Cardiovasc Res. 2023;119:1416–26.
38. Frenis K, Kalinovic S, Ernst BP, Kvandova M, Al Zuabi A, Kuntic M, et al. Long-term effects of aircraft noise exposure on vascular oxidative stress, endothelial function and blood pressure: no evidence for adaptation or tolerance development. Front Mol Biosci. 2021;8:814921.
39. Olbrich HG, Roosli M, Herrmann E, Maschke C, Schadow K, Hahnel T, et al. Aircraft noise exposure and risk for recurrent cardiovascular events after acute coronary syndrome: a prospective patient cohort study. Environ Res. 2023;238:117108.
40. Bayo Jimenez MT, Gericke A, Frenis K, Rajlic S, Kvandova M, Kroller-Schon S, et al. Effects of aircraft noise cessation on blood pressure, cardio- and cerebrovascular endothelial function, oxidative stress, and inflammation in an experimental animal model. Sci Total Environ. 2023;903:166106.
41. Hahad O, Al-Kindi S, Lelieveld J, Munzel T, Daiber A. Supporting and implementing the beneficial parts of the exposome: The environment can be the problem, but it can also be the solution. Int J Hyg Environ Health. 2024;255:114290.
42. Kvandova M, Rajlic S, Stamm P, Schmal I, Mihalikova D, Kuntic M, et al. Mitigation of aircraft noise-induced vascular dysfunction and oxidative stress by exercise, fasting, and pharmacological alpha1AMPK activation: molecular proof of a protective key role of endothelial alpha1AMPK against environmental noise exposure. Eur J Prev Cardiol. 2023;30:1554–68.
43. Casey JA, Morello-Frosch R, Mennitt DJ, Fristrup K, Ogburn EL, James P. Race/ethnicity, socioeconomic status, residential segregation, and spatial variation in noise exposure in the contiguous United States. Environ Health Perspect. 2017;125:077017.
44. Collins TW, Nadybal S, Grineski SE. Sonic injustice: disparate residential exposures to transport noise from road and aviation sources in the continental United States. J Transp Geogr. 2020;82:102604.
45. United States Environmental Protection Agency. Framework for Cumulative Risk Assessment. https://www.epa.gov/risk/framework-cumulative-risk-assessment#:~:text=Cumulative%20risk%20assessment%20is%20an,activities%20related%20to%20cumulative%20risk. Accessed 10 Oct 2024. 2003.
46. Hahad O, Rajagopalan S, Lelieveld J, Sorensen M, Frenis K, Daiber A, et al. Noise and air pollution as risk factors for hypertension: part I-epidemiology. Hypertension. 2023;80:1375–83.
47. European Commission. FUTURE BRIEF: Noise abatement approaches - Issue 17. 2017. https://environment.ec.europa.eu/publications/future-brief-noise-abatement-approaches-issue-17_en. Accessed 10 Oct 2024.
48. Sorensen M, Poulsen AH, Hvidtfeldt UA, Brandt J, Frohn LM, Ketzel M, et al. Air pollution, road traffic noise and lack of greenness and risk of type 2 diabetes: a multi-exposure prospective study covering Denmark. Environ Int. 2022;170:107570.
49. Poulsen AH, Sorensen M, Hvidtfeldt UA, Christensen JH, Brandt J, Frohn LM, et al. Concomitant exposure to air pollution, green space, and noise and risk of stroke: a cohort study from Denmark. Lancet Reg Health Eur. 2023;31:100655.
50. Poulsen AH, Sorensen M, Hvidtfeldt UA, Ketzel M, Christensen JH, Brandt J, et al. Concomitant exposure to air pollution, green space and noise, and risk of myocardial infarction: a cohort study from Denmark. Eur J Prev Cardiol. 2024;31:131–41.
51. Kuntic M, Kuntic I, Krishnankutty R, Gericke A, Oelze M, Junglas T, et al. Co-exposure to urban particulate matter and aircraft noise adversely impacts the cerebro-pulmonary-cardiovascular axis in mice. Redox Biol. 2023;59:102580.
52. Schmidt FP, Basner M, Kroger G, Weck S, Schnorbus B, Muttray A, et al. Effect of nighttime aircraft noise exposure on endothelial function and stress hormone release in healthy adults. Eur Heart J. 2013;34:3508–3514a.
53. Lin MI, Fulton D, Babbitt R, Fleming I, Busse R, Pritchard KA Jr, et al. Phosphorylation of threonine 497 in endothelial nitric-oxide synthase coordinates the coupling of L-arginine metabolism to efficient nitric oxide production. J Biol Chem. 2003;278:44719–26.
54. Fisslthaler B, Loot AE, Mohamed A, Busse R, Fleming I. Inhibition of endothelial nitric oxide synthase activity by proline-rich tyrosine kinase 2 in response to fluid shear stress and insulin. Circ Res. 2008;102:1520–8.
55. Loot AE, Schreiber JG, Fisslthaler B, Fleming I. Angiotensin II impairs endothelial function via tyrosine phosphorylation of the endothelial nitric oxide synthase. J Exp Med. 2009;206:2889–96.
56. Schulz E, Wenzel P, Munzel T, Daiber A. Mitochondrial redox signaling: Interaction of mitochondrial reactive oxygen species with other sources of oxidative stress. Antioxid Redox Signal. 2014;20:308–24.
57. Nguyen TT, Stevens MV, Kohr M, Steenbergen C, Sack MN, Murphy E. Cysteine 203 of cyclophilin D is critical for cyclophilin D activation of the mitochondrial permeability transition pore. J Biol Chem. 2011;286:40184–92.
58. Daiber A, Di Lisa F, Oelze M, Kroller-Schon S, Steven S, Schulz E, et al. Crosstalk of mitochondria with NADPH oxidase via reactive oxygen and nitrogen species signalling and its role for vascular function. Br J Pharm. 2017;174:1670–89.

AUTHOR CONTRIBUTIONS

TM and JLB contributed to the conception of the article. TM conducted the literature review and prepared the draft manuscript. AD, TM, MR, and MK contributed to the research content. JLB provided technical support and policy insight. All authors provided writing support and interpretation of results, and reviewed the manuscript.

FUNDING

A.D. and T.M. were supported by vascular biology research grants from the Boehringer Ingelheim Foundation for the collaborative research group "Novel and neglected cardiovascular risk factors: molecular mechanisms and therapeutics" and through continuous research support from Foundation Heart of Mainz and the Center for Translational Vascular Biology (CTVB). T.M. is a PI and M.K. and A.D. are (young) Scientists of the DZHK (German Center for Cardiovascular Research), partner site

Rhine-Main, Mainz, Germany. The work was also supported by the environmental network EXPOHEALTH funded by the state Rhineland-Palatinate, Germany. Open Access funding enabled and organized by Projekt DEAL.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

Ethical approval was not required for this manuscript. Data used were obtained from the published literature. No data were directly obtained from human subjects.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Thomas Münzel.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

14th ICBEN 2023 18 - 22 JUNE BELGRADE

14th ICBEN Congress on Noise as a Public Health Problem

The effects of aircraft noise on sleep quality, sleepiness and annoyance in individuals sleeping during daytime vs. nighttime

Susanne Bartels[1], Melanie Sorce[1], Lisa Marie Piepenstock[1], Daniel Aeschbach[1]

[1] Department of Sleep and Human Factors Research, Institute of Aerospace Medicine, German Aerospace Center (DLR), Cologne, Germany

Corresponding author's e-mail address: susanne.bartels@dlr.de

EXTENDED ABSTRACT

INTRODUCTION

Nighttime work is a vital factor for the functioning of modern societies [1]. Around 15 % of the population in Germany work night shifts, requiring them to sleep during the day [2]. Night workers often work between 23:00 and 07:00 h [3] and consequently have to sleep at daytime. Due to the circadian misalignment associated with shift work sleep is more fragile [4].

As ample evidence shows, environmental noise, including aircraft noise, can disturb sleep by increasing sleep fragmentation and reducing sleep depth [5]. Moreover, with increasing noise exposure, self-reported sleep quality decreases [5] and annoyance increases [6]. However, evidence exists mostly for the healthy population, whereas less is known about noise effects in vulnerable groups such as shift workers, the elderly and individuals with an illness who may be more susceptible to the adverse effects of noise [7].

Up to now, the effect of noise on daytime sleep has scarcely been investigated. Research on the specific effect of aircraft noise on daytime sleep is lacking completely. The present laboratory study examined the effect of aircraft noise exposure during both nighttime sleep and daytime sleep, with the latter serving as model for intrinsically more fragile sleep. To this end we quantified objective and subjective sleep quality, sleepiness as well as short-term annoyance.

MATERIALS AND METHODS

In the present study, 33 participants (aged 18-40 years; 18 females) slept in the laboratory during two visits that included two consecutive sleep episodes, each. We assigned participants randomly to either a daytime sleep group ("day sleepers") or a nighttime sleep group ("night sleepers"). The two laboratory visits, during one of which participants were exposed to aircraft

noise during both sleep episodes, were separated by a recovery break of at least seven days. During the sleep episodes with aircraft noise exposure, a noise scenario composed by 81 aircraft fly-over sounds from eight different aircraft types was played back in the bedrooms. The resulting energy-equivalent sound pressure level across the time in bed was L_{eq} = 46.8 dB(A) representing a common indoor aircraft noise exposure near Cologne/Bonn Airport, which is a German hub with a 24/7 operation scheme. For the purpose of a typical aircraft noise scenario, we recorded aircraft sounds in an apartment with tilted windows located six km away from the airport and directly under the flight path.

We measured sleep via polysomnography and derived the following sleep parameters: Sleep efficiency, number of awakenings, time spent in sleep stages 1, 2 and slow wave sleep as well as REM sleep. Sleep quality was also assessed via self-reports using a six-item questionnaire.

After getting up, participants rated their acute sleepiness using the Karolinska Sleepiness Scale [8] and their annoyance due to aircraft noise using an adapted version of the 5-point verbal ICBEN scale [9]. Sleepiness assessments were repeated after 10 to 11 hours awake as well as shortly before the next sleep episode.

The effect of aircraft noise exposure on the selected criterion variables were analyzed separately in the daytime sleep and the nighttime sleep group using linear mixed models. We included noise exposure, sleep episode, and an interaction between noise exposure and sleep episode as predictors plus a random intercept for the participants.

RESULTS

Results showed significant effects of aircraft noise exposure on subjective sleep quality and annoyance reported after getting up in both day and night sleepers. Sleepiness averaged across assessment times (after getting up, after 10/11 hours awake, prior to the next sleep episode) was significantly increased after sleep under aircraft noise exposure in day sleepers, but not in night sleepers.

An effect of aircraft noise exposure on sleep efficiency was found neither for night sleepers nor day sleepers. Time spent in sleep stages 1 and 2 was higher under noise exposure in day sleepers, but not in night sleepers. Likewise, the number of awakenings was increased during noise exposure in day sleepers, but not in night sleepers. Noise exposure reduced the time spent in REM sleep and slow wave sleep on a trend level ($p < 0.1$) during noise exposure in day sleepers, but not in night sleepers.

Besides, in day sleepers, an interaction between the noise exposure and the sleep episode was found such that slow wave sleep was reduced in the first but not in the subsequent sleep episode with noise exposure. On a trend level, an interaction between noise exposure and the sleep episode was found for the number of awakenings in day sleepers. Whilst the number of awakenings was higher in the first sleep episode with noise exposure, it was not in the second one. Similarly, we found an interaction for noise annoyance and subjective sleep quality in day sleepers. Annoyance was increased and self-rated sleep quality was decreased in the first noise-exposed sleep episode whilst noise exposure showed no effect in the subsequent sleep episode.

DISCUSSION AND CONCLUSION

The present findings indicate a stronger effect of aircraft noise exposure on participants sleeping during daytime than on participants sleeping during nighttime. The data suggest that

intrinsically more fragile sleep of night workers may be more vulnerable to the effects of transportation noise.

The significant interactions between noise exposure and the sleep episode may indicate that a compensation takes place between the first and the second noise-exposed sleep episode in day sleepers. The loss in slow wave sleep and the higher number of awakenings seem to have activated homeostatic compensatory mechanisms that prevented effects of noise exposure to become manifest during and immediately after the second sleep episode. Lower annoyance scores and higher subjective sleep quality given after the second sleep episode may reflect the assumed compensatory response.

Since the current study investigated the effects of aircraft noise exposure on people who are required to sleep during daytime for the first time, a discussion of the results in the light of previous findings is hardly feasible. However, the current findings warrant further examination of the effect of transportation noise on sleep in night workers, preferably across a longer time span.

REFERENCES

1. Virkkunen H, et al. The triad of shift work, occupational noise, and physical workload and risk of coronary heart disease. Occupational and Environmental Medicine, 2006;63(6):378-386.

2. Statistisches Bundesamt (Destatis). Qualität der Arbeit - Geld verdienen und was sonst noch zählt. 2017, Statistisches Bundesamt. Available at: https://www.destatis.de/DE/Presse/Pressekonferenzen/2017/Arbeitsmarkt/pressebroschuere-Arbeitsmarkt.pdf?__blob=publicationFile&v=2&src=asp-cu&typ=pdf&cid=6200

3. Griefahn B, Marks A, Robens S. Effects of noise on sleep in shift workers. in Proceedings of 20th International Congress on Acoustics, ICA, March 7-12, 2010, Capetown. 2010.

4. Akerstedt T. Shift work and disturbed sleep/wakefulness. Occup Med (Lond), 2003;53(2):89-94.

5. Basner M, McGuire S. WHO environmental noise guidelines for the European region: a systematic review on environmental noise and effects on sleep. Int. J. Environ. Res. Public Health, 2018;15(3):519.

6. Quehl J, Müller U, Mendolia F. Short-term annoyance from nocturnal aircraft noise exposure: results of the NORAH and STRAIN sleep studies. Int Arch. Occup. Environ Health, 2017;90(8):765-778.

7. van Kamp I, Davies H. Noise and health in vulnerable groups: a review. Noise Health, 2013;15:153-159.

8. Akerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. Neuroscience, 1990;52:29-37.

9. Fields JM et al. Standardized general-purpose noise reaction questions for community noise surveys: Research and a recommendation - Community response to noise team of ICBEN. Journal of Sound and Vibration, 2001;242(4): 641-679.

European Heart Journal (2013) **34**, 3508–3514
doi:10.1093/eurheartj/eht269

CLINICAL RESEARCH

Effect of nighttime aircraft noise exposure on endothelial function and stress hormone release in healthy adults

Frank P. Schmidt[1], Mathias Basner[2], Gunnar Kröger[1], Stefanie Weck[1], Boris Schnorbus[1], Axel Muttray[3], Murat Sariyar[4], Harald Binder[4], Tommaso Gori[1], Ascan Warnholtz[1], and Thomas Münzel[1]*

[1]Department of Medicine II, University Medical Center, Johannes Gutenberg University Mainz, Langenbeckstrasse 1, 55131 Mainz, Germany; [2]Unit of Experimental Psychiatry, Division of Sleep and Chronobiology, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA; [3]Institut für Arbeits-, Sozial- und Umweltmedizin, University of Mainz, Mainz, Germany; and [4]Institute for Medical Biometry, Epidemiology and Informatics, University of Mainz, Mainz, Germany

Received 31 January 2013; revised 6 June 2013; accepted 20 June 2013; online publish-ahead-of-print 2 July 2013

See page 3472 for the editorial comment on this article (doi:10.1093/eurheartj/eht339)

Aims Aircraft noise disturbs sleep, and long-term exposure has been shown to be associated with increases in the prevalence of hypertension and an overall increased risk for myocardial infarction. The exact mechanisms responsible for these cardiovascular effects remain unclear.

Methods and results We performed a blinded field study in 75 healthy volunteers (mean age 26 years), who were exposed at home, in random order, to one control pattern (no noise) and two different noise scenarios [30 or 60 aircraft noise events per night with an average maximum sound pressure level (SPL) of 60 dB(A)] for one night each. We performed polygraphy during each study night. Noise caused a worsening in sleep quality ($P < 0.0001$). Noise60, corresponding to equivalent continuous SPLs of 46.3 dB (Leq) and representing environmental noise levels associated with increased cardiovascular events, caused a blunting in FMD ($P = 0.016$). As well, although a direct comparison among the FMD values in the noise groups (control: 10.4 ± 3.8%; Noise30: 9.7 ± 4.1%; Noise60: 9.5 ± 4.3%, $P = 0.052$) did not reach significance, a monotone dose-dependent effect of noise level on FMD was shown ($P = 0.020$). Finally, there was a priming effect of noise, i.e. the blunting in FMD was particularly evident when subjects were exposed first to 30 and then to 60 noise events ($P = 0.006$). Noise-induced endothelial dysfunction (ED) was reversed by the administration of Vitamin C ($P = 0.0171$). Morning adrenaline concentration increased from 28.3 ± 10.9 to 33.2 ± 16.6 and 34.1 ± 19.3 ng/L ($P = 0.0099$). Pulse transit time, reflecting arterial stiffness, was also shorter after exposure to noise ($P = 0.003$).

Conclusion In healthy adults, acute nighttime aircraft noise exposure dose-dependently impairs endothelial function and stimulates adrenaline release. Noise-induced ED may be in part due to increased production in reactive oxygen species and may thus be one mechanism contributing to the observed association of chronic noise exposure with cardiovascular disease.

Keywords Endothelial function • Aircraft noise • Cardiovascular risk

Introduction

The WHO estimates that in high-income Western European countries (population ~340 million) at least 1 million healthy life years are lost every year due to environmental noise.[1] The negative health outcomes of noise include annoyance,[2] sleep disturbance,[3] cardiovascular disease,[4,5] and impairment of cognitive performance in children.[6]

Aircraft noise has been shown to be more annoying than road- and railway noise at the same equivalent noise level.[7] Epidemiologic studies have demonstrated associations between long-term

* Corresponding author. Tel: +49 6131 17 7250, Fax: +49 6131 17 6615, Email: tmuenzel@uni-mainz.de

exposure to aircraft noise and an increased incidence of arterial hypertension and therefore cardiovascular disease.[7,8] The mechanisms underlying these adverse cardiovascular effects of aircraft noise are not fully understood. Nocturnal noise exposure seems to be more relevant for the genesis of cardiovascular disease than daytime noise exposure,[9] probably due to repeated autonomic arousals that have been shown to habituate to a lesser degree to noise than, e.g. cortical arousals.[10] In general, the risk increases with exposure duration, and is higher in those who decide to sleep with open windows.[11,12]

Undisturbed sleep of sufficient length is obligatory for the maintenance of daytime performance and health.[13] The human organism recognizes, evaluates, and reacts to environmental sounds even while asleep.[14] These reactions are part of an integral activation process of the organism that expresses itself, e.g. as changes in sleep structure or increases in blood pressure and heart rate.[10,15] Environmental noise may decrease the restorative power of sleep by means of repeatedly occurring activations (so-called *sleep fragmentation*) that are associated with more awakenings/arousals, less deep sleep and rapid eye movement sleep, and early awakenings in the morning. Although healthy subjects have been shown to habituate to aircraft noise exposure to a certain degree,[10] the habituation is not complete, and noise-induced awakenings and, especially, activations of the autonomic nervous system can still be observed in subjects that have been exposed to aircraft noise for several years.[16] Sleep disturbance and especially sleep restriction in turn have been shown to cause hormonal and metabolic changes,[17–19] which could predispose to a future development of cardiovascular disease.

Circadian changes related to altered sleep may also adversely affect the immune system[20,21] and may increase the responsiveness of the heart to hypertrophic stimuli.[22] Although plausible, the link between polysomnographic evidence of sleep disturbance during aircraft noise exposure and cardiovascular outcomes is not well established. It is largely unknown which changes or indices predict long-term risk.[23]

Furthermore, polysomnography (i.e. the simultaneous measurement of the electroencephalogram, electrooculogram, and electromyogram) is a complex and cumbersome method, which is not very well suited for larger studies in the general population.[24] Therefore, other methods, like actigraphy (a non-invasive technique to monitor human rest/activity cycles) and behaviourally confirmed awakenings, have been used in this context.

In the case of aircraft noise, hypertension may be a consequence of the noise-induced release of stress hormones such as epi- and norepinephrine and/or the development of vascular (endothelial) dysfunction. Endothelial dysfunction (ED) is considered an early step in the development of atherosclerotic changes of the vasculature (for review see[25]) and can be assessed non-invasively. Recent studies indicate that in patients with coronary artery disease and hypertension, ED assessment in the forearm may have prognostic implications.[25]

Based on these considerations, the primary aim of the present study was to test whether nocturnal exposure to aircraft noise may induce ED. The morning plasma level of adrenaline was a secondary endpoint. In a subgroup of noise 60 subjects, we also tested whether acute vitamin C challenges may improve ED.

Methods

The study was approved by the ethics committee of University Medical Center Mainz. All participants were volunteers and signed informed consent. Anti-aircraft noise activists were excluded from the study as were persons with high nighttime traffic noise exposure at home as determined by noise maps available from municipal online resources ($L_{A,eq,22\text{-}6h} > 40$ dB for aircraft noise and $L_{A,eq,22\text{-}6h} > 45$ dB for road and rail traffic noise).

Study population

The study enrolled 75 healthy non-smokers between 20 and 60 years of age. Before the study, audiometry was performed in all participants. Persons with an age-adjusted hearing loss of 20 dB or more on one or both ears were excluded from the study. Subjects with sleep disorders [score >10 on the Pittsburgh Sleep Quality Index (PSQI)][26] or psychiatric disorders (assessed by M.I.NI. Screen interview) were also ineligible. Study participants were instructed to refrain from consumption of coffee, tea, alcohol, sleep altering medications, and nicotine on the day prior to the study night. Otherwise, they were told to continue their usual diet and daily routines. Hormonal contraception was allowed but care was taken to synchronize study nights with the hormonal status. Other hormonal therapies were excluded.

Study procedures

After inclusion, participants returned to the laboratory for three visits. During the night preceding each visit, subjects were exposed in a randomized order to one of three noise patterns. One night served as the control night, and subjects were exposed to normal background noise. During the other two nights, subjects were exposed to recording reproducing different numbers of flights: Noise30 with playback of 30 aircraft noise events, and Noise60 with playback of 60 aircraft noise events. Study visits were prescheduled with at least three non-study nights between two study nights and on the same weekday if possible. In premenopausal women, the visits were scheduled to occur in the same phase of the hormonal cycle. Supplemental vitamins, alcohol, and caffeine containing beverages were prohibited on the evening and night before the study.

Participants were randomly given one of six different sequences of noise and control nights according to the randomization plan (C-30-60, C-60-30, 30-C-60, 30-60-C, 60-C-30, 60-30-C). At study onset, subjects and investigators were both blinded to the noise pattern sequence. Participants slept in their usual home environment and were asked to maintain their usual sleep–wake rhythm. They wore portable polygraphic screening devices (SOMNOwatch™ plus, SOMNOmedics, Randersacker, Germany) during the night with continuous recording of ECG, SpO_2, actimetry, light, and derived parameters as described in previous studies.[27–29]

In the noise exposure nights, the same aircraft noise event was played back repeatedly. It was originally recorded in the bedroom of a resident living in the vicinity of Düsseldorf airport (window tilted open), and was already used in previous studies on the effects of aircraft noise on sleep.[30,31] Noise patterns were recorded as MP3 files and played back on a standard portable audio system with a fixed speaker position relative to the head of the subject. The playback volume was levelled at each measurement site to guarantee similar SPLs at all study sites. During the night, the SPL was continuously recorded in the bedroom with class-2 sound level meters (Datalogger DL-160S, Voltcraft, Germany; Model 407764A Datalogger, Extech Instruments, USA) to assure subject compliance. They were placed on the nightstand close to the participants. All sound files were coded with a study number and were of equal length and file size, making inadvertent unblinding less likely. All noise patterns started with a constant tone of 30 s duration to allow

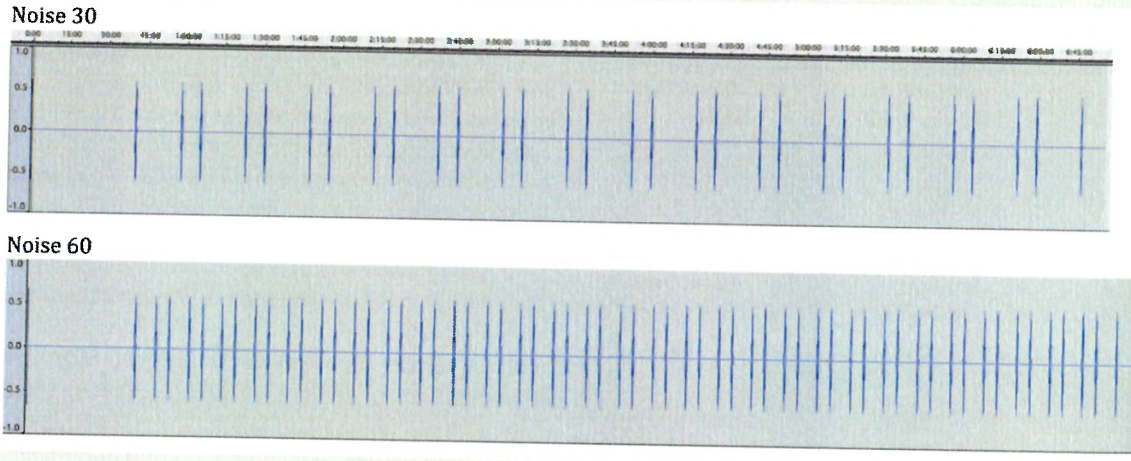


Figure 1 Schematic representation of the noise events.

testing of equipment function. The first aircraft noise event was played back after 39.5 min to facilitate sleep onset. The last aircraft noise event was played back after 415 min. Each noise event lasted roughly 45 s. Noise events followed a short–long–short pattern with time between events roughly 6:40 min and 16:40 min for Noise30 and 4:05 min and 6:40 min for Noise60 (*Figure 1*).

After the study night, participants returned to the study centre in a fasting state for further testing. Flow-mediated dilatation of the brachial artery was measured at the same time in the early morning and before 10 a.m. by a technician using standardized techniques described previously.[25,32,33] Briefly, brachial artery diameter is measured with a linear ultrasound probe at rest and after a 5 min occlusion period with a pressure cuff. Changes in diameter are given in percent and reflect the endothelial release of vasodilatory substances such as nitric oxide (NO). To address the role of reactive oxygen species in causing ED, FMD was also measured in a subset of five subjects exposed to Noise60 before and after administration of vitamin C (2 g, p.o.) as previously described.[34] After FMD measurement, blood samples were drawn and questionnaires were filled out. Blood samples were transported directly to a clinical laboratory for evaluation. Part of the blood was centrifuged, aliquoted, and frozen at below −62 °C for later testing. Global noise sensitivity was measured using the Dortmund Noise Sensitivity Questionnaire.[35] The Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ)[36] was used to assess individual chronotype. Pulse transit time (PTT, time between the R wave in the ECG and peak oxygen saturation measured at the tip of the first finger of the right hand) and heart rate accelerations (number of accelerations >20 bpm and >2 s per h) were calculated. Interleukin-6 and cortisol were measured in serum with chemiluminescence immunoassay. Adrenaline was measured from NH4-heparine anticoagulated blood drawn 30 min after puncture and cooled during transport to the lab.

Statistical analysis

The primary endpoint of the study was the change in %FMD induced by the different levels of noise. Secondary outcomes included the changes in all variables measured (neurohormones, PTT, inflammatory markers, etc), the existence of a relationship between dose of noise and blunting of FMD (dose–effect relationship), and whether Noise30 or Noise60 had a priming effect on the blunting in FMD induced by, respectively, Noise60 or Noise30. A separate study was conducted to test the effect of Vitamin C on FMD in subjects exposed to Noise60. Data are presented as mean ± standard deviation. The Kolmogorov–Smirnov test was used to assess whether the data were normally distributed. To address the primary endpoint, we first compared the effect of Noise60, which reproduces the increase in night noise previously shown to be associated with an increased incidence of cardiovascular events and prevalence of hypertension,[9] with the control visit. Further, a multi-factor ANOVA [taking into account noise exposure, night of exposure, and subject id (for subject-related differences)] was performed. A test for a monotone effect of the exposure (dose of nighttime aircraft noise: 0, 30, or 60) was performed by using exposure as a pseudo-continuous factor in the ANOVA. Further, a (*post hoc*) multi-factor ANOVA was performed with two additional factors: one for the comparison of FMD values after Noise60 in all subjects allocated to control–Noise30–Noise60 or Noise30–Noise60–control to FMD values of all other patients, and the other for the same comparison after Noise30 in all subjects exposed to Noise60 directly preceding Noise30. *P*-values <0.05 were considered significant. All tests were two-sided. *P*-values for secondary outcome variables are shown without adjustment for multiple testing. Based on the paper by Ghiadoni *et al.*,[37] a difference between means of 2% could be expected (with SD of about 3%). With a sample size of 75 and a standard deviation of FMD differences between Noise60 and control of 3%, one may expect to detect a FMD difference of 0.98% with a power of 80% at the alpha-level 0.05.

Results

Study population and setting

A total of 88 subjects were enrolled. Thirteen of them were excluded from the final analysis. Reasons for dropouts (3 study subjects before and 10 after the first study night) included the diagnosis of hyperthyroidism, relocation to noise-affected areas, protocol violations, and inadequate data recording quality. The study subjects included in the final analysis were on average 26 years (range 20–54 years) old, 61% were females. FMD data could not be analysed for one visit in two subjects. The study population did not have relevant sleep disorders as assessed with the PSQI, and had a moderate

Table 1 Baseline characteristics of the study population

Age	(min–max)	25.7 (20–54)
Gender	% female	61.3
Height	cm	174.6 ± 10.2
Weight	kg	67.7 ± 11.9
BMI	kg/m^2	22.1 ± 2.4
Baseline noise sensitivity, chronotype, sleep quality index		
NoiSeQ	0–3	1.22 ± 0.38
Horne–Östberg	14–86	49.41 ± 9.79
PSQI	0–21	3.73 ± 1.72
Laboratory values		
Total cholesterol	mg/dL	182.9 ± 32.9
LDL	mg/dL	104.7 ± 25.6
HDL	mg/dL	60.7 ± 15.3
Triglycerides	mg/dL	87.2 ± 41.9
C-reactive protein	mg/L	1.3 ± 1.5
Creatinin	mg/dL	1.0 ± 0.5
HbA1C	%	5.3 ± 0.5

Data are presented as mean ± SD.
NoiSeQ, Dortmund Noise Sensitivity Questionnaire with three greatest noise sensitivity; Horne-Östberg, Morningness-Eveningness Questionnaire; PSQI, Pittsburgh Sleep Quality Index.

trend towards evening chronotype (characteristics shown in *Table 1*). None reported significant diseases.

The average maximum SPL of aircraft noise events recorded in participants' bedrooms is presented in *Table 2*. Overall nighttime SPLs had average peak levels of 49.6 dB(A) (control), 59.9 dB(A) (Noise30), and 60.9 dB(A) (Noise60) (both $P < 0.0001$ compared with control). Corresponding equivalent continuous SPLs Leq(3) were 35.4 dB(A), 43.1 dB(A), and 46.3 dB(A), respectively. The mean time between awakening and start of image acquisition for FMD did not differ across visits ($P > 0.5$).

Control and noise exposure nights did not differ significantly with regard to outside and body temperatures, total time in bed or subjective well being prior to the study night (data not shown). All data were normally distributed.

Haemodynamic changes in response to night noise

As a secondary predefined endpoint, we also found a dose-dependent decrease in minimum PTT (*Table 2*) after the noise nights, which was mirrored by the changes in systolic blood pressure ($P = 0.11$ for the changes among visits, *Table 2*). Automated heart rate analysis detected no significant change in mean and maximum heart rate. Heart rate acceleration index as detected by the polygraphic device did not differ between noise exposure and control nights.

With increasing number of noise events, study subjects reported deteriorating sleep quality in the morning after the respective study night ($P = 0.001$).

Effects of nocturnal noise on endothelial function

The comparison of the FMD values measured after the control visit and the Noise60 visit demonstrated a blunting in endothelial responses after noise ($P = 0.016$). When all three levels of noise were compared, and noise exposure (0, 30, 60) was used as a pseudo-continuous covariate in the AN(C)OVA in order to test for a dose-dependency in the effect of noise on FMD, a linear relationship between FMD values and exposure was found ($P = 0.020$), confirming that the exposure to more severe noise causes more severe ED. Although a standard comparison among the three noise levels within the ANOVA, i.e. without assuming a monotone effect for dose as a pseudo-continuous covariate, did not reach statistical significance (control night: 10.4 ± 3.8%; after 30 noise events: 9.7 ± 4.1%; after 60 noise events: 9.5 ± 4.3%, $P = 0.052$, *Figure 2A*), the introduction of the two additional factors described in the Methods section evidenced a priming effect of Noise30 nights on the blunting in FMD induced by Noise60 ($P = 0.006$), i.e. Noise60 had the largest impact on FMD in the subjects who had already been exposed to Noise30. Finally, there was no effect of the randomization sequence (means after each visit adjusted for the effect of effect of noise: first visit: 9.8%, second visit: 10.0%, third visit: 9.4%, $P = 0.757$).

Noise had no effect on blood flow and reactive hyperaemia (control: 855 ± 357%; Noise30: 900 ± 423%; Noise60: 900 ± 389%, $P = 0.55$). As well, baseline arterial diameter did not significantly influence the effect of noise on FMD.

In order to study the mechanism of the blunting in FMD induced by Noise60, we tested the impact of acute challenges with vitamin C in five control subjects. In these subjects, 2 h after the administration of Vitamin C, FMD was markedly improved (*Figure 2B*, $P = 0.0171$). In contrast, in a separate control group of subjects exposed to Noise60 without Vitamin C, FMD did not change as an effect of time (11.21 ± 5.56%; FMD at 2 h: 11.47 ± 5.80%; $P = 0.842$).

Effects of night noise on neurohormones and markers of inflammation (*Table 2*)

We found a marked increase in plasma adrenaline concentrations between control and Noise30 and 60 exposure nights, respectively (control: 28.3 ± 10.9 ng/L; Noise30: 33.2 ± 16.6; Noise60: 34.1 ± 19.3 ng/L, $P = 0.0099$, *Figure 3*) In contrast, morning plasma levels of cortisol did not increase with noise exposure. Likewise, inflammatory markers IL-6 and C-reactive protein were unaffected by noise exposure.

Discussion

We demonstrate cardiovascular effects of nighttime aircraft noise in young and healthy individuals with low cardiovascular risk. Nighttime aircraft noise increased plasma epinephrine levels, worsened sleep quality, and decreased pulse transit time, a parameter of arterial stiffness, which varies inversely to arterial blood pressure. A dose-dependent decrease in endothelial function after exposure to increasing levels of noise was also observed. Acute Vitamin C challenges improved endothelial function in a separate group of subjects exposed to Noise60. We found no effect of aircraft noise

Table 2 Effects of nighttime noise on the quality of sleep, haemodynamic parameters, cortisol levels, and inflammation parameters

	Control	Noise 30	Noise 60	*P* (ANOVA)
PeakdB(A)	48.63 ± 3.47	59.89 ± 3.28	60.87 ± 2.46	<0.001
Leq3dB(A)	35.44 ± 8.08	43.12 ± 4.91	46.28 ± 3.89	<0.001
Sleep quality	6.70 ± 1.92	5.20 ± 2.28	4.37 ± 2.23	<0.001
Movement index	3.94 ± 5.40	3.06 ± 2.85	3.23 ± 3.44	0.639
Haemodynamic parameters				
HR mean	58.7 ± 7.6	59.5 ± 7.7	59.7 ± 7.8	0.345
HR max	102.6 ± 13.3	104.3 ± 13.2	106.9 ± 17.5	0.325
BPsys mean (mmHg)	109.8 ± 15.4	114.9 ± 13.9	115.2 ± 12.4	0.120
BP rise Index	2.3 ± 2.3	2.5 ± 2.32	3.8 ± 5.9	0.397
HR_accel Index	25.8 ± 32.4	22.8 ± 23.0	23.9 ± 26.5	0.215
Pulse transit time (ms)	271.8 ± 12.3	270.9 ± 18.7	264.9 ± 15.7	0.003
Laboratory parameters				
Adrenaline (ng/L)	28.3 ± 10.9	33.2 ± 16.6	34.1 ± 19.3	0.010
Cortisol (μg/L)	15.34 ± 5.47	16.43 ± 5.55	15.76 ± 5.78	0.197
Neutrophils (%)	51.0 ± 11.39	49.77 ± 9.48	50.04 ± 7.87	0.353
IL-6 (pg/mL)	2.6 ± 3.45	2.27 ± 1.25	2.57 ± 3.29	0.383
C-reactive protein (mg/L)	2.26 ± 6.30	2.27 ± 4.82	1.55 ± 2.16	0.512

Data are presented as mean ± SD.
Leq3 dB, long-term equivalent continuous sound level; PTT, pulse transit time; BP, blood pressure; HR accel, heart rate acceleration; IL-6, interleukin 6.

exposure on nocturnal motility, heart rate or blood cortisol, neutrophils, IL-6, or C-reactive protein.

Interestingly, a priming effect of aircraft noise on ED was observed, i.e. previous exposure to Noise30 caused Noise60 to have larger effects on endothelial function. These data demonstrate that aircraft noise can affect endothelial function, and that rather than habituation, prior exposure to noise seems to amplify the negative effect of noise on endothelial function. Although the mechanisms of these observations cannot be characterized at a molecular level *in vivo* in humans, it has been previously shown that other forms of mental stress lead to a decrease in endothelial function.[37–40] With regards to the molecular mechanisms, previous studies indicate that noise leads to an up-regulation, rather than a downregulation, of the eNOS.[41] Interestingly, such an increased eNOS activity does not necessarily result in improved endothelial responses. For instance, in animal models of diabetes and/or hypertension, increased expression of an uncoupled (superoxide-producing) eNOS is associated with impaired endothelial function (reviewed in[42]). Since measurements of NO and/or superoxide production in the local vascular microenvironment are impossible to perform in humans, this question cannot be addressed at the present time. The improvement in FMD observed in our study 2 h after application of the antioxidant vitamin C in subjects exposed to Noise60 is compatible with this evidence, and it suggests that exposure to aircraft noise might lead to ED due to increased vascular oxidative stress.[34]

We also demonstrate changes in PTT, a parameter that correlates inversely with changes in blood pressure. Briefly, PTT is measured as the time it takes a pulse wave to travel between two arterial sites. Rises in blood pressure cause vascular tone to increase, leading to increased arterial stiffness and a shorter PTT. As mentioned above, these data are compatible with those of the HYENA project, in which an increase prevalence of hypertension was reported in subjects exposed to nocturnal noise in the range of 50 dB (similar to our Noise60 condition; 46.3 dB).[9] Similarly, acute noise events were associated in this study with increased systolic and diastolic blood pressure by 6.2 and 7.4 mmHg, a phenomenon which, interestingly, was not necessarily associated with awakenings.

With regard to the pathophysiological mechanism behind the changes in blood pressure and vascular function, we also report elevated epinephrine levels after exposure to noise. It has been demonstrated that intermittent release of adrenaline may be implicated in the development of hypertension.[43] Epinephrine is released as a response to different stressors such as noise[44] and increases the release and the effects of norepinephrine.[45] Interestingly, increased epinephrine levels have been found in patients with borderline hypertension,[45,46] suggesting a role in the early history of hypertension.

Importantly, increased plasma catecholamines have also been shown to correlate negatively with endothelial function as measured by FMD.[47] A recent study has linked autonomic sympathetic activation to the development of hypertension in elderly patients independent of the cause of activation of the autonomic nervous system.[48]

Our results are congruent with the growing amount of data linking short sleep duration or sleep disturbances of various kinds to the development of cardiovascular disease. For example, shift work has been shown to cause impaired endothelial function, sympathetic activation, and metabolic changes.[49,50] Extensive evidence exists for the relation between obstructive sleep apnoea, hypertension, ED, and

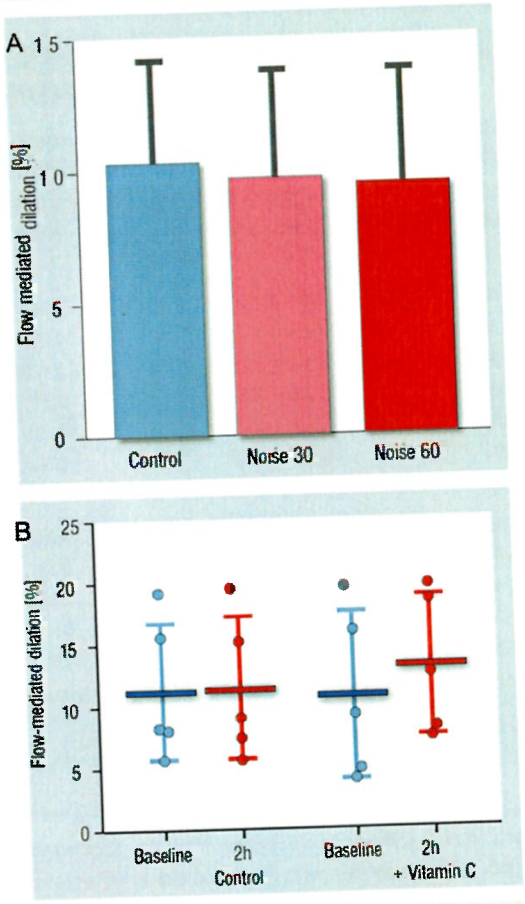


Figure 2 (A) Effects of Noise30 and Noise60 on flow-mediated dilation (FMD). Data are mean ± SD; $P = 0.020$ for a test using the level of noise a pseudo-continuous variable, demonstrating a linear relationship between FMD values and noise exposure. (B) Effects of Vitamin C (2 g, p.o.) in FMD of the brachial artery. 2 h after Vitamin C administration, the antioxidant improved significantly FMD in five control subjects exposed to Noise60. Date are presented as mean ± SD; $P = 0.0171$ for the effect of Vitamin C on FMD, paired t-test.

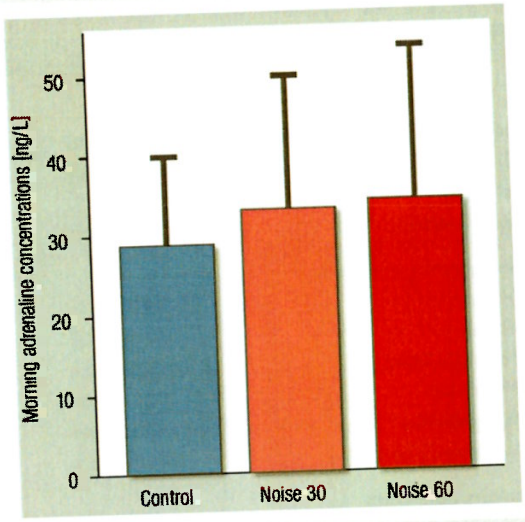


Figure 3 Effects of Noise30 and Noise60 on plasma adrenaline levels. Nighttime noise exposure significantly increases circulating catecholamine levels. Data are mean ± SD. $P < 0.01$, ANOVA.

subsequently cardiovascular disease.[51] Recently, the restless legs syndrome has been identified as another cause for sleep disruption, and it has been shown to increase the risk for myocardial infarction in women.[52] There is ample evidence that nocturnal aircraft noise exposure disturbs and fragments sleep, leads to changes in sleep structure, increases sleepiness during the following day, and leads to impairments of cognitive performance.[10,23,53,54] The results of our study suggest that these changes in sleep structure negatively affect the cardiovascular system, and that these changes, in the case of long-term exposure, may predispose to the development of hypertension and cardiovascular disease.

The study by design eliminated noise adaptation processes, which can often mask effects of environmental influences. Therefore, it is unclear whether the negative cardiovascular effects observed in this study persist after weeks or months with continued noise exposure. However, biologic adaptation is often incomplete and requires physiologic resources therefore also putting strain on the system as a whole. Effects of aircraft noise in population-based studies are likely to be mitigated by partial physiologic adaptation and avoidance of residential areas with high levels of noise exposure by highly sensitive individuals. Other environmental factors like air pollution, which has also been shown to influence endothelial function,[55] may interfere with noise effects in epidemiological studies. Therefore, data from interventional studies may be helpful in judging the effect of nocturnal noise on cardiovascular health and disease.

Limitatio nsof the study

The protocol was designed as a field study with minimal sleep disruption due to environment and equipment, thus creating ecologically valid conditions. We avoided on purpose a pure laboratory environment where ambient conditions, sound levels, and external stimuli can be controlled at the expense of creating artificial rather than familiar conditions. Sleep quality is very sensitive to changes in surroundings and study subjects usually show more pronounced alterations of sleep in the laboratory than in the field.[56] There were no adaptation nights prior to study nights due to logistic constraints and because, since subjects were not required to sleep in non-familiar environments, our study design did not demand such adaptation. Reinforcing this, the analysis did not show a significant first-night effect for our primary outcome,[57] which supports the validity of our study design and results. Study subjects were healthy, young, and with a female majority and are therefore not representative of the whole population. In general, younger adults usually show less sleep problems and disturbance than older persons when exposed to noise, and the fact that noise had an impact also on such a low-risk population rather emphasizes the potential clinical relevance of the present

findings. Finally, endothelium-independent vasodilation was not systematically measured and the data are not presented: nitroglycerin responses were measured initially, but these measures were discontinued due to refusal by many study participants related to the side effects of the drug.

Summary and conclusions

In a group of young and healthy volunteers, we found evidence for significant impairment of endothelial function after only one night of aircraft noise exposure with 60 noise events. Pointing to a significant contribution of oxidative stress in this phenomenon, these adverse changes of the vasculature were markedly improved by acute Vitamin C challenges. Endothelial dysfunction was paralleled by significant increases in circulating adrenaline levels and a substantial, dose-dependent decrease in sleep quality and an increase in systolic blood pressure. These findings indicate that hypertension observed in response to nighttime exposure to noise might be explained by increased sympathetic activation but also by the occurrence of vascular dysfunction. Accumulating data increasingly confirms that sleep disturbance of different causes might represent a novel, important health risk. An undisturbed night's sleep is important for health and well-being and should be protected as far as possible, and reducing nocturnal aircraft noise can therefore be regarded as a preventive measure for cardiovascular disease. Since the present studies demonstrate adverse effects of endothelial function and stress hormones in healthy adults, the implications for patients with known cardiovascular disease will need to be tested in further studies.

Funding

The Study was funded by the Foundation Heart of Mainz, the Rober Müller Foundation and the Department of Cardiology of the University Medical Center Mainz. T.G. receives a Grant from the Federal Ministry of Education and Research (within project BMBF 01EO1003).

Conflict of interest: none declared.

References

1. Fritschi L, Brown AL, Kim R, Schwela DH, Kephalopoulos S. Burden of disease from environmental noise, World Health Organization. 2011. http://www.euro.who.int/__data/assets/pdf_file/0008/136466/e94888.pdf.
2. Miedema HME, Oudshoorn CGM. Annoyance from transportation noise: relationships with exposure metrics DNL and DENL and their confidence intervals. *Environ Health Perspect* 2001;**109**:409–416.
3. Muzet A. Environmental noise, sleep and health. *Sleep Med Rev* 2007;**11**:135–142.
4. van Kempen E, Babisch W. The quantitative relationship between road traffic noise and hypertension: a meta-analysis. *J Hypertens* 2012;**30**:1075–1086.
5. Sörensen M, Andersen ZJ, Nordsborg RB, Jensen SS, Lillelund KG, Beelen R, Schmidt EB, Tjonneland A, Overvad K, Raaschou-Nielsen O. Road traffic noise and incident myocardial infarction: a prospective cohort study. *PLoS ONE* 2012;**7**:1–7.
6. Stansfeld SA, Matheson MP. Noise pollution: non-auditory effects on health. *Br Med Bull* 2003;**68**:243–257.
7. Miedema HM, Oudshoorn CG. Annoyance from transportation noise: relationships with exposure metrics DNL and DENL and their confidence intervals. *Environ Health Perspect* 2001;**109**:409–416.
8. Rosenlund M, Berglind N, Pershagen G, Jarup L, Bluhm G. Increased prevalence of hypertension in a population exposed to aircraft noise. *Occup Environ Med* 2001;**58**:769–773.
9. Jarup L, Babisch W, Houthuijs D, Pershagen G, Katsouyanni K, Cadum E, Dudley ML, Savigny P, Seiffert I, Swart W, Breugelmans O, Bluhm G, Selander J, Haralabidis A, Dimakopoulou K, Sourtzi P, Velonakis M, Vigna-Taglianti F. Hypertension and Exposure to Noise near Airports: the HYENA study. *Environ Health Perspect* 2008;**116**:329–333.
10. Basner M, Müller U, Elmenhorst E-M. Single and combined effects of air, road, and rail traffic noise on sleep and recuperation. *Sleep* 2011;**34**:11–23.
11. Lercher P, Widmann U, Kofler W. Transportation noise and blood pressure: the importance of modifying factors. In Cassereau D, ed. *Proceedings of the 29th International Congress and Exhibition on Noise Control Engineering*. Nice, France: Sociéte Francaise d, Acoustique 2000, pp. 2071–2075.
12. Huss A, Spoerri A, Egger M, Roosli M. Aircraft noise, air pollution, and mortality from myocardial infarction. *Epidemiology* 2010;**21**:829–836.
13. Banks S, Dinges DF. Behavioral and physiological consequences of sleep restriction. *J Clin Sleep Med* 2007;**3**:519–528.
14. Oswald I, Taylor AM, Treisman M. Discriminative responses to stimulation during human sleep. *Brain* 1960;**83**:440–453.
15. Basner M, Müller U, Griefahn B. Practical guidance for risk assessment of traffic noise effects on sleep. *Appl Acoustics* 2010;**71**:518–522.
16. Basner M, Isermann U, Samel A. Aircraft noise effects on sleep: application of the results of a large polysomnographic field study. *J Acoust Soc Am* 2006;**119**:2772–2784.
17. Schmid SM, Hallschmid M, Jauch-Chara K, Wilms B, Lehnert H, Born J, Schultes B. Disturbed glucoregulatory response to food intake after moderate sleep restriction. *Sleep* 2009;**34**:371–377.
18. Wehrens SM, Hampton SM, Finn RE, Skene DJ. Effect of total sleep deprivation on postprandial metabolic and insulin responses in shift workers and non-shift workers. *J Endocrinol* 2010;**206**:205–215.
19. Broussard JL, Ehrmann DA, Van Cauter E, Tasali E, Brady MJ. Impaired insulin signaling in human adipocytes after experimental sleep restriction: a randomized, crossover study. *Ann Intern Med* 2012;**157**:549–557.
20. Lange T, Dimitrov S, Fehm HL, Westermann J, Born J. Shift of monocyte function toward cellular immunity during sleep. *Arch Intern Med* 2006;**166**:1695–1700.
21. Dimitrov S, Lange T, Nohroudi K, Born J. Number and function of circulating human antigen presenting cells regulated by sleep. *Sleep* 2007;**30**:401–411.
22. Durgan DJ, Tsai JY, Grenett MH, Pat BM, Ratcliffe WF, Villegas-Montoya C, Garvey ME, Nagendran J, Dyck JR, Bray MS, Gamble KL, Gimble JM, Young ME. Evidence suggesting that the cardiomyocyte circadian clock modulates responsiveness of the heart to hypertrophic stimuli in mice. *Chronobiol Int* 2011;**28**:187–203.
23. Basner M, Van den Berg M, Griefahn B. Aircraft noise effects on sleep: mechanisms, mitigation and research needs. *Noise Health* 2010;**12**:95–109.
24. Basner M, Brink M, Elmenhorst EM. Critical appraisal of methods for the assessment of noise effects on sleep. *Noise Health* 2012;**14**:321–329.
25. Munzel T, Sinning C, Post F, Warnholtz A, Schulz E. Pathophysiology, diagnosis and prognostic implications of endothelial dysfunction. *Ann Med* 2008;**40**:180–196.
26. Zisberg A, Gur-Yaish N, Shochat T. Contribution of routine to sleep quality in community elderly. *Sleep* 2010;**33**:509–514.
27. Gesche H, Grosskurth D, Kuchler G, Patzak A. Continuous blood pressure measurement by using the pulse transit time: comparison to a cuff-based method. *Eur J Appl Physiol* 2012;**112**:309–315.
28. Bartsch S, Ostojic D, Schmalgemeier H, Bitter T, Westerheide N, Eckert S, Horstkotte D, Oldenburg O. Validation of continuous blood pressure measurements by pulse transit time: a comparison with invasive measurements in a cardiac intensive care unit. *Dtsch Med Wochenschr* 2010;**135**:2406–2412.
29. Pepin JL, Delavie N, Pin I, Deschaux C, Argod J, Bost M, Levy P. Pulse transit time improves detection of sleep respiratory events and microarousals in children. *Chest* 2005;**127**:722–730.
30. Basner M, Samel A. Nocturnal aircraft noise effects. *Noise Health* 2004;**6**:83–93.
31. Basner M, Samel A, Isermann U. Aircraft noise effects on sleep: application of the results of a large polysomnographic field study. *J Acoust Soc Am* 2006;**119**:2772–2784.
32. Ostad MA, Eggeling S, Tschentscher P, Schwedhelm E, Boger R, Wenzel P, Meinertz T, Munzel T, Warnholtz A. Flow-mediated dilation in patients with coronary artery disease is enhanced by high dose atorvastatin compared to combined low dose atorvastatin and ezetimibe: results of the CEZAR study. *Atherosclerosis* 2009;**205**:227–232.
33. Warnholtz A, Wild P, Ostad MA, Elsner V, Stieber F, Schinzel R, Walter U, Peetz D, Lackner K, Blankenberg S, Munzel T. Effects of oral niacin on endothelial dysfunction in patients with coronary artery disease: results of the randomized, double-blind, placebo-controlled INEF study. *Atherosclerosis* 2009;**204**:216–221.
34. Gokce N, Keaney JF Jr, Frei B, Holbrook M, Olesiak M, Zachariah BJ, Leeuwenburgh C, Heinecke JW, Vita JA. Long-term ascorbic acid administration reverses endothelial vasomotor dysfunction in patients with coronary artery disease. *Circulation* 1999;**99**:3234–3240.
35. Schutte M, Marks A, Wenning E, Griefahn B. The development of the noise sensitivity questionnaire. *Noise Health* 2007;**9**:15–24.
36. Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol* 1976;**4**:97–110.

37. Ghiadoni L, Donald AE, Cropley M, Mullen MJ, Oakley G, Taylor M, O'Connor G, Betteridge J, Klein N, Steptoe A, Deanfield JE. Mental stress induces transient endothelial dysfunction in humans. *Circulation* 2000;**102**:2473–2478.
38. Harris CW, Edwards JL, Baruch A, Riley WA, Pusser BE, Rejeski WJ, Herrington DM. Effects of mental stress on brachial artery flow-mediated vasodilation in healthy normal individuals. *Am Heart J* 2000;**139**:405–411.
39. Spieker LE, Hurlimann D, Ruschitzka F, Corti R, Enseleit F, Shaw S, Hayoz D, Deanfield JE, Luscher TF, Noll G. Mental stress induces prolonged endothelial dysfunction via endothelin-a receptors. *Circulation* 2002;**105**:2817–2820.
40. Chen Y, Dangardt F, Osika W, Berggren K, Gronowitz E, Friberg P. Age- and sex-related differences in vascular function and vascular response to mental stress. Longitudinal and cross-sectional studies in a cohort of healthy children and adolescents. *Atherosclerosis* 2012;**220**:269–274.
41. Heinrich UR, Selivanova O, Feltens R, Brieger J, Mann W. Endothelial nitric oxide synthase upregulation in the guinea pig organ of corti after acute noise trauma. *Brain Res* 2005;**1047**:85–96.
42. Forstermann U, Munzel T. Endothelial nitric oxide synthase in vascular disease: from marvel to menace. *Circulation* 2006;**113**:1708–1714.
43. Brown MJ, Macquin I. Is adrenaline the cause of essential hypertension? *Lancet* 1981; **2**:1079–1082.
44. Andren L, Hansson L, Bjorkman M, Jonsson A. Noise as a contributory factor in the development of elevated arterial pressure. A study of the mechanisms by which noise may raise blood pressure in man. *Acta Med Scand* 1980;**207**:493–498.
45. Nezu M, Miura Y, Adachi M, Kimura S, Toriyabe S, Ishizuka Y, Ohashi H, Sugawara T, Takahashi M. The effects of epinephrine on norepinephrine release in essential hypertension. *Hypertension* 1985;**7**:187–195.
46. Nezu M, Miura Y, Adachi M, Kimura S, Toriyabe S, Ishizuka Y, Ohashi H, Sugawara T, Takahashi M. The role of epinephrine in essential hypertension. *Jpn Circ J* 1983;**47**: 1242–1246.
47. Kaplon RE, Walker AE, Seals DR. Plasma norepinephrine is an independent predictor of vascular endothelial function with aging in healthy women. *J Appl Physiol* 2011; **111**:1416–1421.
48. Dauphinot V, Barthelemy JC, Pichot V, Celle S, Sforza E, Achour-Crawford E, Gosse P, Roche F. Autonomic activation during sleep and new-onset ambulatory hypertension in the elderly. *Int J Cardiol* 2011;**155**:155–159.
49. Amir O, Alroy S, Schliamser JE, Asmir I, Shiran A, Flugelman MY, Halon DA, Lewis BS. Brachial artery endothelial function in residents and fellows working night shifts. *Am J Cardiol* 2004;**93**:947–949.
50. Wehrens SM, Hampton SM, Skene DJ. Heart rate variability and endothelial function after sleep deprivation and recovery sleep among male shift and non-shift workers. *Scand J Work Environ Health* 2011;**38**:171–181.
51. Levy P, Tamisier R, Arnaud C, Monneret D, Baguet JP, Stanke-Labesque F, Dematteis M, Godin-Ribuot D, Ribuot C, Pepin JL. Sleep deprivation, sleep apnea and cardiovascular diseases. *Front Biosci (Elite Ed)* 2012;**4**:2007–2021.
52. Li Y, Walters AS, Chiuve SE, Rimm EB, Winkelman JW, Gao X. Prospective study of restless legs syndrome and coronary heart disease among women. *Circulation* 2012; **126**:1689–1694.
53. Elmenhorst EM, Elmenhorst D, Wenzel J, Quehl J, Mueller U, Maass H, Vejvoda M, Basner M. Effects of nocturnal aircraft noise on cognitive performance in the following morning: dose-response relationships in laboratory and field. *Int Arch Occup Environ Health* 2010;**83**:743–751.
54. Basner M. Nocturnal aircraft noise increases objectively assessed daytime sleepiness. *Somnologie* 2008;**12**:110–117.
55. Krishnan RM, Adar SD, Szpiro AA, Jorgensen NW, Van Hee VC, Barr RG, O'Neill MS, Herrington DM, Polak JF, Kaufman JD. Vascular responses to long- and short-term exposure to fine particulate matter: MESA Air (Multi-Ethnic Study of Atherosclerosis and Air Pollution). *J Am Coll Cardiol* 2012; **60**:2158–2166.
56. Pearsons K, Barber D, Tabachnick BG, Fidell S. Predicting noise-induced sleep disturbance. *J Acoust Soc Am* 1995;**97**:331–338.
57. Agnew HW Jr, Webb WB, Williams RL. The first night effect: an EEG study of sleep. *Psychophysiology* 1966;**2**:263–266.

Review

A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP10197.

Environmental Noise and Effects on Sleep: An Update to the WHO Systematic Review and Meta-Analysis

Michael G. Smith,[1]* *Makayla Cordoza,*[1] *and Mathias Basner*[1]

[1]Unit for Experimental Psychiatry, Division of Sleep and Chronobiology, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA

Background: Nighttime noise carries a significant disease burden. The World Health Organization (WHO) recently published guidelines for the regulation of environmental noise based on a review of evidence published up to the year 2015 on the effects of environmental noise on sleep.

Objectives: This systematic review and meta-analysis will update the WHO evidence review on the effects of environmental noise on sleep disturbance to include more recent studies.

Methods: Investigations of self-reported sleep among residents exposed to environmental traffic noise at home were identified using Scopus, PubMed, Embase, and PsycINFO. Awakenings, falling asleep, and sleep disturbance were the three outcomes included. Extracted data were used to derive exposure–response relationships for the probability of being highly sleep disturbed by nighttime noise [average outdoor A-weighted noise level (L_{night}) 2300–0700 hours] for aircraft, road, and rail traffic noise, individually. The overall quality of evidence was assessed using Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) criteria.

Results: Eleven studies ($n = 109{,}070$ responses) were included in addition to 25 studies ($n = 64{,}090$ responses) from the original WHO analysis. When sleep disturbance questions specifically mentioned noise as the source of disturbance, there was moderate quality of evidence for the probability of being highly sleep disturbed per 10-dB increase in L_{night} for aircraft [odds ratio (OR) = 2.18; 95% confidence interval (CI): 2.01, 2.36], road (OR = 2.52; 95% CI: 2.28, 2.79), and railway (OR = 2.97; 95% CI: 2.57, 3.43) noise. When noise was not mentioned, there was low to very low quality of evidence for being sleep disturbed per 10-dB increase in L_{night} for aircraft (OR = 1.52; 95% CI: 1.20, 1.93), road (OR = 1.14; 95% CI: 1.08, 1.21), and railway (OR = 1.17; 95% CI: 0.91, 1.49) noise. Compared with the original WHO review, the exposure–response relationships closely agreed at low (40 dB L_{night}) levels for all traffic types but indicated greater disturbance by aircraft traffic at high noise levels. Sleep disturbance was not significantly different between European and non-European studies.

Discussion: Available evidence suggests that transportation noise is negatively associated with self-reported sleep. Sleep disturbance in this updated meta-analysis was comparable to the original WHO review at low nighttime noise levels. These low levels correspond to the recent WHO noise limit recommendations for nighttime noise, and so these findings do not suggest these WHO recommendations need revisiting. Deviations from the WHO review in this updated analysis suggest that populations exposed to high levels of aircraft noise may be at greater risk of sleep disturbance than determined previously. https://doi.org/10.1289/EHP10197

Introduction

Sleep is a vital component of human life that serves many critical roles in physical and mental health and well-being.[1] Sufficient quantity and quality of sleep are requirements for optimal daytime alertness and performance, and high quality of life.[2] Experimental studies suggest that restricted sleep duration causes blood vessel dysfunction,[3] induces changes in glucose metabolism[4,5] and appetite regulation,[6] and impairs memory consolidation.[7] Accordingly, epidemiological studies have consistently found that chronic short or interrupted sleep is associated with negative health outcomes, including obesity,[8] diabetes,[9] hypertension,[10] cardiovascular disease,[11] all-cause mortality,[12] and poorer cognitive function.[13] Chronic insufficient or disrupted sleep is therefore of public health relevance, and sleep disturbance is considered a major adverse consequence of exposure to environmental noise.[14]

In Europe, there is a substantial burden of disease from environmental noise, primarily from aircraft, road, and rail traffic.[15,16] In 2011, the World Health Organization (WHO) attributed the majority of this disease burden to noise-induced sleep disturbance, with 903,000 disability-adjusted life years lost annually in Western Europe alone.[14] Environmental noise is also a problem outside of Europe, for example, recent data from the U.S. Bureau of Transportation Statistics estimates that 41.7 million people in the United States are exposed to air and road traffic noise at 24-h average levels ($L_{AEq,24h}$) >50 dB.[17] This noise level, per conversion data from Brink et al.[18] is equivalent to a nighttime (2300–0700 hours) level of 45.3 dB (L_{night}), which is around or above the level associated with adverse effects on sleep.[15] Nighttime noise can fragment sleep structure by inducing awakenings and shifts to lighter, less restorative sleep.[19] Importantly, these effects do not seem to habituate fully, and arousals and awakenings induced by aircraft noise can occur even among chronically exposed individuals.[20–22] Although noise-induced sleep fragmentation and reductions in total sleep time are less severe than in sleep restriction studies, sleep disturbance by chronic noise exposure may lead to the development of disease in the long term. Experimental studies have found adverse effects of nocturnal aircraft noise on parameters of endothelial function, oxidative stress, and inflammation.[23,24] This points to the importance of noise-induced sleep disturbance for cardiovascular disease risk, and, indeed, this is supported with epidemiological data where nighttime noise is more strongly associated with indicators of vascular stiffness and hypertension compared with daytime noise.[25] The ubiquity of exposure to environmental noise in industrialized nations, and the chronic nature of that exposure, therefore poses a significant threat to health.[26]

*Current address: Michael G. Smith, Department of Occupational and Environmental Medicine, School of Public Health and Community Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden.

Address correspondence to Mathias Basner, 1019 Blockley Hall, 423 Guardian Dr., Philadelphia, PA 19104 USA. Email: basner@pennmedicine.upenn.edu

Supplemental Material is available online (https://doi.org/10.1289/EHP10197).

M.C. is supported by the National Institutes of Health (K99 NR019862). All other authors declare they have nothing to disclose.

Received 25 August 2021; Revised 3 May 2022; Accepted 9 May 2022; Published 11 July 2022.

In 2018, the WHO published recommendations for protecting human health from exposure to environmental noise.[15] These guidelines included strong recommendations for target nighttime noise levels to mitigate adverse effects of traffic noise on sleep, which were 45 dB L_{night} for road traffic, 44 dB L_{night} for rail traffic, and 40 dB L_{night} for air traffic. These recommendations were based primarily on a systematic review and meta-analysis on the effects of noise on sleep, which included studies published up to the year 2015 only.[19] There has been continued and substantial interest and research in the domain of noise and sleep during the intervening years. We therefore updated the earlier systematic review and meta-analysis to include studies published up to the year 2021. This updated analysis is restricted to field studies on the effects of nocturnal traffic noise on self-reported sleep in adults, and it has the overarching aim of synthesizing updated exposure–response relationships for the probability of being highly sleep disturbed.

Methods

This review and analysis was prepared following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement guidelines.[27] The completed PRISMA checklist is given in Table S1. The review and analysis protocol was defined *a priori* and registered in PROSPERO (record CRD42021229587) before conducting any preliminary searches, screening of articles, or data extraction. The University of Pennsylvania institutional review board (IRB) determined that the study did not meet the definition of human subjects research given that no identifiable information was being obtained, and therefore review or approval of the study by the IRB was not required.

The analytic approach is described in detail below and was consistent with the previous WHO review,[19] with the following exceptions: *a*) Exposures were limited to traffic noise from aircraft, road, and rail traffic, and *b*) effects on sleep were limited to self-reported questionnaire outcomes. These form the basis of the highly sleep disturbed exposure–response relationships and calculations of the burden of disease by noise and are, therefore, are critical outcomes from a noise policy perspective. Studies on acute noise-induced awakenings using objective measures, such as actigraphy or polysomnography, were not included.

Eligibility Criteria

Studies were restricted to primary investigations in humans exposed to environmental noise from aircraft, road, and rail traffic at home. Studies investigating other sources, such as wind turbine noise or hospital noise, were excluded. Studies were eligible only if sound pressure levels were measured or predicted at the participant's home. Studies with subjective evaluation of the noise levels, distance to the noise source as a surrogate measure of noise level, or noise levels not specific to a participant's home address were excluded. A minimum of two different noise level categories were required so that exposure–response relationships for sleep disturbance could be constructed.

Studies were eligible if they employed prospective, retrospective, cohort, longitudinal, cross-sectional, or case–control study designs. Laboratory studies, intervention studies, or studies in which noise was introduced artificially were excluded due to low generalizability in real-world settings. Studies were restricted to original research published or accepted for publication in the year 2000 or later. Article language was restricted to English, Dutch, French, and German.

This review and analysis focuses on self-reported sleep disturbance by traffic noise. Eligible studies included at least one of the three most common outcomes of self-reported disturbance that were identified in the original WHO review[19]:

- Awakenings from sleep
- The process of falling asleep
- Sleep disturbance

Studies were eligible if they either explicitly mentioned noise as the source of disturbance, for example, "How often is your sleep disturbed by noise from aircraft?", or included more general sleep questions that did not explicitly mention noise, for example, "How often do you have difficulties sleeping?". So that the probability of being highly sleep disturbed could be determined, eligible studies were required to include outcome scales that indicated either the severity or the frequency of symptoms or disturbance on a nonbinary scale. A binary response scale was, however, permitted if the phrasing of the question was such that a binary response would indicate being highly sleep disturbed, for example, "Is your sleep highly disturbed by noise from road noise?". Studies reporting other measures of self-reported sleep not described above (e.g., perceived sleep quality, estimated total sleep time, morning sleepiness), and studies on objective sleep (e.g., polysomnography, actigraphy) or sleep medication use, were excluded.

Study Selection

All studies identified in the WHO evidence review[19] for which data were already available for meta-analysis were included in the updated synthesis. We also identified studies published later than the WHO review from a scoping synthesis by van Kamp et al.[28] Because van Kamp et al.[28] included studies published up to June 2019 only, we further searched four electronic databases (Scopus, PubMed, Embase, PsycINFO), to identify more recent relevant studies published up to 31 December 2021. This search was done with the same search terms and strategy from van Kamp et al.[28] that were relevant for traffic noise and self-reported sleep. The full electronic search strategy is given in Table S2. Any studies of which we were aware but that were not identified during the literature search were also screened for eligibility.

Two reviewers (M.G.S. and M.C.) independently and manually screened the title and abstract of each identified study against the study eligibility criteria. If eligibility could not be determined from the title and abstract alone, the full text was reviewed. Any differences in eligibility judgments were resolved by discussion and consensus, with input from a third reviewer (M.B.) if needed.

Data Extraction and Synthesis

The following variables were extracted by a single investigator from the original records for review by the authorship team: article title, authors, publication year, traffic mode, noise level, noise metric and time base, noise exposure methodology, sleep disturbance question(s) and response scale(s), study design, country, city, effective sample size, number of data points per respondent, and sleep disturbance point estimates. If data could not be extracted directly from the published articles and supplemental materials, we directly contacted all study authors for whom contact details were available to request data. We requested a list of relevant questions on sleep and the response scales used, the total number of respondents in 5-dB bins, and the percentage of respondents reporting being highly sleep disturbed in each 5-dB bin. We requested only these summary data, and no identifiable information on any study respondents was requested or obtained. If the study authors did not reply after they were sent two reminders, the contact was considered a nonresponse and the study was excluded.

The exposure variable of interest for the meta-analysis was average nighttime outdoor A-weighted noise level from a single traffic mode (air, road, and rail) during the night, hereafter termed L_{night}, measured in decibels. A-weighting is a filter network that is used to simulate the nonlinear frequency response of human hearing. The night period was defined as 2300–0700 hours, in line with EU Environmental Noise Directive 2002/49/EC.[29] In studies where noise levels were reported as a different metric, we converted to L_{night} using the conversion formulae from Brink et al.[18] given below. L_{night} was not treated as a continuous variable but, rather, was categorized into 5-dB bins, following the approach used in the WHO review.[19] For open-ended noise level categories, we assigned a noise level that was 2.5 dB above or below the cutoff, for instance, <50 dB and >50 dB would be coded as 47.5 dB and 52.5 dB, respectively. The midpoints of each 5-dB bin were used as the noise exposure levels in the statistical analyses.

The primary outcome of interest was the probability of self-reporting high sleep disturbance for a given noise level. We *a priori* defined three separate domains of questions that were used to determine sleep disturbance. First, "awakenings from sleep," referring to the period between sleep onset and final awakening. These awakenings are defined as events where a participant wakes from sleep, regains consciousness, and recalls the awakening the following morning. Second, the "process of falling asleep," defined as the transition from wakefulness to sleep. Third, "sleep disturbance," defined as the internal or external interference with sleep onset or sleep continuity. Included studies had to address at least one of these domains in the form of at least one self-reported question. For each of these three question types, the coding of whether a respondent was highly sleep disturbed depended on the response scale used. For responses using 5- or 11-point scales referring to the severity of the disturbance, the top two and top three categories were, respectively, defined as highly sleep disturbed, following previous conventions for the International Commission on the Biological Effects of Noise (ICBEN) annoyance scale.[30] For responses that referred to the frequency of symptoms, a frequency of "often" or at least three times per week was considered as highly sleep disturbed because this frequency of difficulty sleeping is a diagnostic criterion of insomnia.[31] One study used a dichotomous filter question, "Do you have any trouble with your sleep?", to determine if a respondent would answer a question on the frequency of difficulty falling asleep.[32] Any responses of "no" to this filter question were coded as not highly sleep disturbed.

Study-Specific Exposure and Response Characterization

One study reported noise exposure as 24-h average levels ($L_{AEq,24h}$).[33] These noise levels were converted to L_{night} using the following conversion equations[18]:

$$\text{Road traffic: } L_{night(23\text{–}07)} = L_{AEq,24h} - 4.7\,\text{dB, and}$$

$$\text{Railway traffic: } L_{night(23\text{–}07)} = L_{AEq,24h} - 0.6\,\text{dB.}$$

One study reported road noise as the day-evening-night level (L_{den}),[34] which was converted to L_{night} as follows[18]:

$$L_{night(23\text{–}07)} = L_{den} - 8.3\,\text{dB.}$$

One study reported noise level as Livello di Valutazione del Aeroportuale (LVA),[35] which is similar to the day-night level (L_{dn}), except that the night period is 7 h (2300–0600 hours) rather than 8 h.[36] Formulae to convert directly from LVA to L_{night} are unavailable; therefore, we made the following assumptions in converting to L_{night}: The 1-h shorter night when using LVA means that the same exposure assessed as L_{dn} will be lower because L_{dn} applies a 10-dB penalty to the night period. We assume −0.7 dB given that that is the difference in L_{dn} metrics with a 1-h difference in the night period (8 vs. 9 h) for aircraft noise.[18] We then incorporated this difference into an appropriate conversion equation to convert from LVA to L_{night}[18]:

$$L_{dn} = \text{LVA} - 0.7\,\text{dB}; L_{night(23\text{–}07)} = L_{dn} - 8.9\,\text{dB, and}$$

$$\therefore L_{night(23\text{–}07)} = \text{LVA} - 0.7\,\text{dB} - 8.9\,\text{dB} = \text{LVA} - 9.6\,\text{dB.}$$

One study used a noise category that was 10-dB-wide (65–75 dB LVA).[35] We subdivided these data into 5-dB-wide bins, assuming $(n)/2$ respondents in each bin (35 respondents per bin) and the same prevalence of high sleep disturbance in each bin as in the 10-dB-wide category.

Two studies assessed noise exposure as both calculated long-term outdoor noise levels and measured indoor noise levels over 3–6 nights.[20,21] We used the calculated outdoor noise levels as the exposure metric to be consistent with other studies in the meta-analysis.

In one study,[21] sleep in the previous night was assessed repeatedly over several mornings. Because of these repeated measures, we first calculated the probability of being highly disturbed using all five to six responses per respondent. We then used these probabilities to determine the number of individuals that would have reported being highly sleep disturbed if only one response was obtained per person. In this way, each respondent contributed only a single data point to the analysis.

One study calculated exposure to railway traffic as including noise from trains, trams, and subways.[37] The questions regarding "sleep disturbance by tram/subway noise" and "sleep disturbance by train noise" in this study were therefore averaged into a single sleep disturbance variable.

Risk of Bias and Quality of Evidence

The risk of bias at the outcome level within individual studies was assessed using the methodology developed within the WHO review,[19] with the following two amendments to the assessment criteria (Table 1). First, in line with recommendations for cross-sectional studies by the National Institutes of Health,[38] a study was considered at high risk of selection bias if the response rate was <50%, down from the 60% criterion in the WHO review. Second, bias due to the sleep measurement outcome was not assessed because our updated analysis focused on only a single sleep measurement outcome (sleep questionnaires), whereas the WHO review included also heart rate or blood pressure, actigraphy, polysomnography, and other objective physiologic measurements. The risk of bias in each domain was assessed independently by two investigators (M.G.S. and M.C.). All studies were included in the meta-analysis regardless of the bias assessment.

To evaluate heterogeneity between studies, we calculated odds ratios (ORs) for each outcome within each study using binary logistic regression in SPSS (version 26; IBM Corp.). For consistency with the WHO review,[19] the range of L_{night} was not restricted in this analysis. Forest plots for all outcomes across studies were generated using RevMan (version 5.4.1; Cochrane Collaboration) using an inverse-variance (IV) random effects method. Heterogeneity between studies for each outcome was assessed using the I^2 statistic. We interpreted I^2 values using thresholds defined by the Cochrane Collaboration.[39] Publication bias across studies was investigated using funnel plots of the individual study estimates.

The quality of evidence across studies for the effects of exposure to aircraft, road, and rail traffic noise on self-reported sleep outcomes where noise was specified, and self-reported sleep outcomes where noise was not specified, was assessed independently

Table 1. Criteria for assessing risk of bias of individual studies (adapted from the WHO review[19]).

Bias domain	Criteria	Risk of bias
A. Selection bias	Random sampling, areas selected based on noise exposure. ≥50% response rate.[a]	Low
	inclusion criteria not contingent on sleep and health conditions a. <50% response rate,[a] or b. Non-random sampling, or c. Sampling not based on noise exposure, or d. Individuals were excluded based on sleep and health criteria	High
	Insufficient information to make a judgment	Unclear
B. Information bias (exposure assessment)	a. Based on measurements for at least 1 wk, or b. Based on a noise map that was verified by noise measurements, or c. Based on a noise map that was based on actual traffic data	Low
	a. Based on measurements of <1 wk, or measurements were not continuous, or b. Based on a noise map that was not verified by noise measurements, or the predictions were not based on actual traffic data	High
	Insufficient information to make a judgment	Unclear
C. Bias due to confounding	All most-important confounders accounted for in analysis	Low
	No accounting for important confounders	High
	Insufficient information to make a judgment	Unclear
D. Reporting bias	Complete reporting of all outcomes analyzed including nonsignificant results	Low
	Not all outcomes reported, underreporting methods or statistical analysis, not reporting conflicts of interest	High
	Insufficient information to make a judgment	Unclear

Note: WHO. World Health Organization.
[a]The 50% response rate criterion was based on recommendations for cross-sectional studies by the National Institutes of Health.[38]

by two investigators using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) criteria.[40] Any differences in the risk of bias assessments for individual studies, or in the quality of evidence across studies for each outcome (GRADE), were resolved by consensus with input from a third investigator if needed.

Meta-Analytic Approach

The primary goal of the meta-analysis was to generate updated exposure–response relationships for the probability of high sleep disturbance for each of the three disturbance types (awakenings, falling asleep, and sleep disturbance) for each traffic mode (air, road, and rail). In line with the WHO review,[19] we also generated a combined estimate for high sleep disturbance across the three different types of disturbance questions, using the following approach: If a study included two or three relevant sleep disturbance questions, the combined estimate was calculated by averaging the responses to those questions for each respondent within a study. This approach was adopted so that each respondent would contribute only a single data point to the analysis of each separate outcome. If a study included only one sleep outcome, the combined estimate and the single study outcome assessed would be the same.

Data for individual studies were provided directly by the authors of each study, binned in 5-dB-wide noise categories. One line of data was created for each sleep disturbance question from each study respondent. For instance, if a study had 500 respondents in the noise category with a 47.5 dB L_{night} midpoint, and 10% were classified as highly sleep disturbed, we generated 450 data lines with non-highly sleep disturbed respondents (binary outcome = 0) and 50 data lines with highly sleep disturbed respondents (binary outcome = 1). Each data line also carried the midpoint of the 5-dB L_{night}-exposure category, a three-level categorical variable for traffic mode (air, road, and rail), a dichotomous variable indicating whether questionnaire data originated from questions that did or did not explicitly mention noise as a source of disturbance in the question for each traffic mode, dichotomous study location indicated a European or non-European study, and a study identification number.

Statistical Analysis

Exposure–response relationships were generated with the following approach: Random study effect logistic regression models with L_{night} (midpoint of the noise exposure category) as the only explanatory variable were performed with the NLMIXED procedure in SAS (version 9.4; SAS Institute, Inc.). This approach accounts for the fact that respondents were clustered within studies, and the weight of a study increases with its sample size. Analyses were restricted to levels between 40 and 65 dB L_{night} because of inaccuracy in predicting noise levels <40 dB and that the highest exposure limit common to all three traffic modes was 65 dB L_{night}. Separate regression models were run stratified by the three traffic modes (air, road, or rail), four sleep disturbance outcome (awakenings, falling asleep, sleep disturbance, or combined estimate of all questions within a study), and the dichotomous noise-specificity of the disturbance question (noise mentioned or noise not mentioned), yielding a total $3 \times 4 \times 2 = 24$ separate regression analyses. Estimate statements were used to generate point estimates and 95% confidence intervals (CIs). Data are reported as dose–response curves and as ORs per 10-dB increase in L_{night}.

To investigate whether a response differed depending between European and non-European studies location, we added study location as a covariate to the logistic regression model and repeated the analysis for the combined estimates of sleep disturbance. These analyses were restricted to the four outcomes where both European and non-European data were available.

We performed a sensitivity analysis to investigate the risks of exposure bias on sleep disturbance. We repeated the logistic regression for the combined estimates of sleep disturbance, restricted between 40–65 dB L_{night}, and stratified analysis by studies that were judged to have a low or high risk of bias in the exposure assessment.

Results

Study Selection

Study identification, screening and selection are summarized in Figure 1. All 25 studies in the WHO review were included.[19] Twenty-one studies published between January 2014 and June

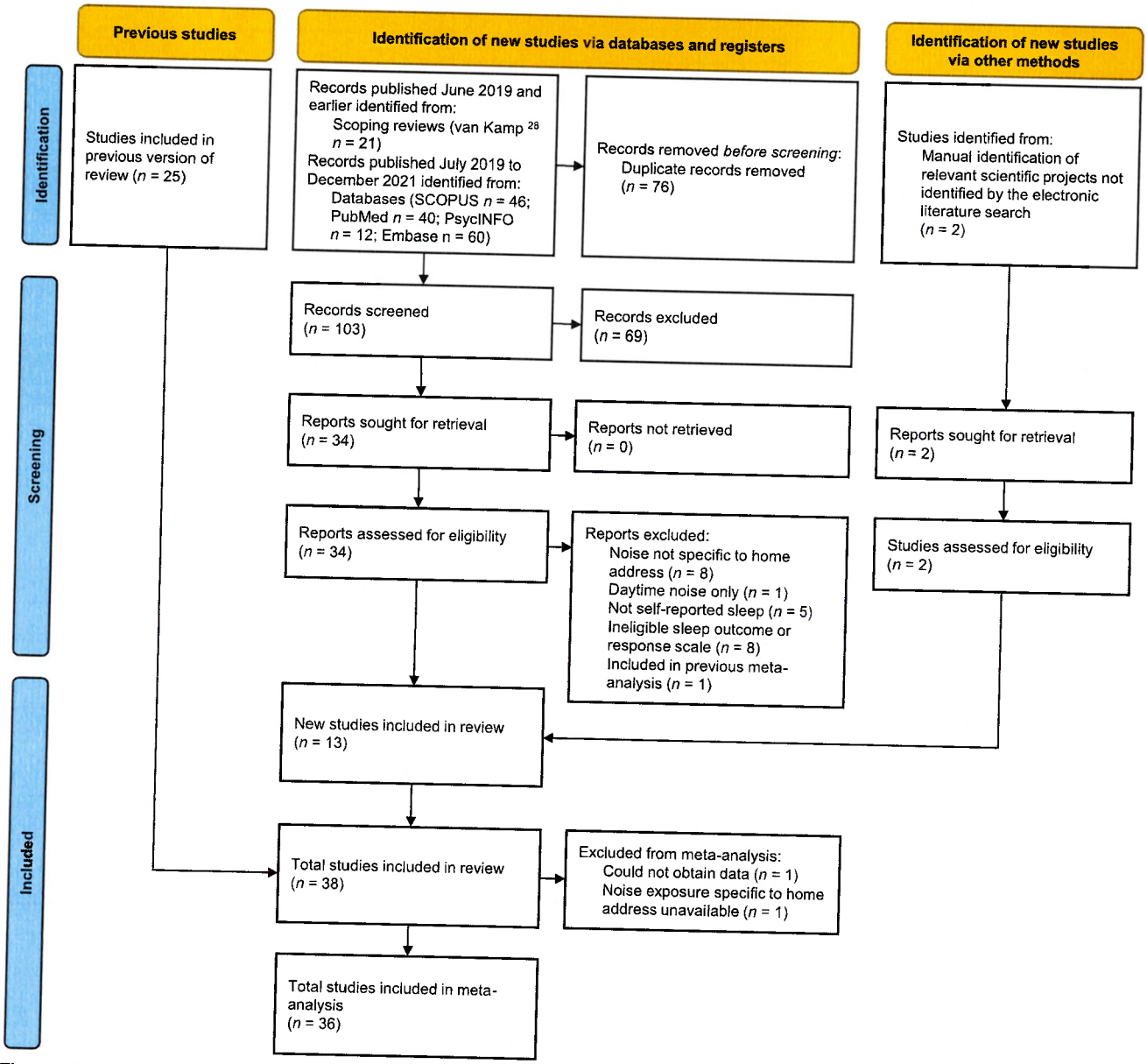


Figure 1. Flow diagram of study identification, screening, and selection. "Study" refers to a data collection campaign including a defined group of participants and one or more outcomes. In one instance, a study was reported in multiple articles[41,42] and is counted as $n = 1$ study. "Report" is a journal article, preprint, conference abstract, study register entry, clinical study report, dissertation, unpublished manuscript, government report, or other document supplying relevant information about a particular study or studies.

2019 were identified by van Kamp et al.[28] Our electronic search additionally identified 82 studies published later than June 2019, after excluding duplicates. After assessing the abstracts and, if needed, the full texts, 11 new studies eligible for the meta-analysis were identified. We also manually identified a further 2 studies that were not identified by the electronic literature searches [the UK Survey of Noise Attitudes (Civil Aviation Authority)[41] and German Noise-Related Annoyance, Cognition and Health (NORAH)[42] projects]. We manually extracted the study documents from project webpages[41,42] and judged both studies to be eligible for inclusion after undergoing the standard screening protocol.

Two studies initially deemed eligible could not be included in the meta-analysis[43,44] because data could not be obtained or noise exposure specific to the home address was unavailable (Table S3). We therefore identified 11 studies in total published since the WHO review to include in the meta-analysis,[20,21,32,34,35,37,41,42,45–47] in addition to the 25 studies included in the original review[19] (Tables 2–4).

Comparison with Previous WHO Review

The effective sample size for each sleep outcome and for each traffic mode, determined using all data in the updated analysis (responses from the WHO analysis plus the 11 newly identified studies) is compared against the sample sizes from the WHO analyses in Figure 2. Sample sizes for the combined estimates where responses to multiple questions were averaged within

Table 2. Studies on exposure to aircraft noise and self-reported sleep outcomes (adapted from the WHO review[19]).

Outcome	Study	N	Location	Disturbance question and responses	Noise metric, (level range)
Awakenings: noise mentioned (total $N = 4{,}613$)	Nguyen et al.[32,a]	559	Hanoi, Vietnam	In daily life, how much do you feel disturbed when an aircraft passes by in the following cases: When you are awakened in your sleep? Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2200–0600 hours (32.5–62.5 dB)
	Nguyen et al.[48]	1,093	Hanoi, Vietnam	In daily life, when an aeroplane passes by, to what degree are you disturbed in the following cases: When you are awakened in your sleep? Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2200–0600 hours (37.5–57.5 dB)
	Yano et al.[49]	776	Hanoi, Vietnam	Same as above	L_{night}, 2200–0600 hours (37.5–57.5 dB)
	Nguyen et al.[50]	511	Da Nang City, Vietnam	Same as above	L_{night}, 2200–0600 hours (37.5–57.5 dB)
	Nguyen et al.[51,52]	804	Hanoi, Vietnam	Same as above	L_{night}, 2200–0600 hours (37.5–52.5 dB)
	Nguyen et al.[53]	870	Ho Chi Minh City, Vietnam	Same as above	L_{night}, 2200–0600 hours (42.5–62.5 dB)
Falling asleep: noise mentioned (total $N = 27{,}869$)	Nguyen et al.[32,a]	545	Hanoi, Vietnam	In daily life, how much do you feel disturbed when an aircraft passes by in the following cases: When it makes it difficult for you to fall asleep? Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2200–0600 hours (32.5–62.5 dB)
	NORAH[42,a]	3,505	Frankfurt, Germany 2011	In the last 12 months aircraft noise has disturbed you when falling asleep? Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2200–0600 hours (32.5–57.5 dB)
	NORAH[42,a]	3,502	Frankfurt, Germany 2012	Same as above	L_{night}, 2200–0600 hours (32.5–67.5 dB)
	NO RAH[42a]	3,505	Frankfurt, Germany 2013	Same as above	L_{night}, 2200–0600 hours (32.5–62.5 dB)
	NORAH[42,a]	5,527	Berlin, Germany 2012	Same as above	L_{night}, 2200–0600 hours (32.5–52.5 dB)
	NORAH[42,a]	2,947	Cologne-Bonn, Germany 2013	Same as above	L_{night}, 2200–0600 hours (32.5–67.5 dB)
	NORAH[42,a]	1,970	Stuttgart, Germany 2013	Same as above	L_{night}, 2200–0600 hours (32.5–52.5 dB)
	Nguyen et al.[48]	1,095	Hanoi, Vietnam	In daily life, when an aeroplane passes by, at what degree are you disturbed in the following cases: When it makes it difficult for you to fall asleep? Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2200–0600 hours (37.5–57.5 dB)
	Yano et al.[49]	780	Hanoi, Vietnam	Same as above	L_{night}, 2200–0600 hours (37.5–57.5 dB)
	Nguyen et al.[50]	512	Da Nang City, Vietnam	Same as above	L_{night}, 2200–0600 hours (37.5–52.5 dB)
	Nguyen et al.[51,52]	805	Hanoi, Vietnam	Same as above	L_{night}, 2200–0600 hours (37.5–52.5 dB)
	Nguyen et al.[53]	868	Ho Chi Minh City, Vietnam	Same as above	L_{night}, 2200–0600 hours (42.5–62.5 dB)
	Schreckenberg et al.[54]	2,308	Germany	How much has aircraft noise in the last 12 months disturbed falling asleep? Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2200–0600 hours (37.5–57.5 dB)
Sleep disturbance: noise mentioned (total $N = 27{,}773$)	Rocha et al.[45,a]	396	Atlanta, Georgia, USA	Thinking about the last 12 months or so, when you were at home, how much was your sleep disturbed by noise from aircraft? Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2300–0700 hours (37.5–52.5 dB)
	Brink et al.[46,a]	2,925	Switzerland	Thinking about the last twelve months at your home, during nighttime when you want to sleep, how much did aircraft noise bother, disturb, or annoy you? Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2300–0700 hours (22.5–62.5 dB)
	Civil Aviation Authority[41,a]	1,200	United Kingdom	Thinking about the summer, when you were here at home, what number from 0 to 10 best shows the degree to which your sleep was disturbed by noise from aeroplanes? Not at all disturbed (0) to Extremely disturbed (10) (HSD 8,[b] 9,[b] 10[b])	L_{night} 2300–0700 hours, summer (37.5–62.5 dB)
	NORAH[42,a]	3,505	Frankfurt, Germany 2011	In the last 12 months aircraft noise has disturbed you when sleeping in the night? Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2200–0600 hours (32.5–57.5 dB)

Table 2. (*Continued.*)

Outcome	Study	*N*	Location	Disturbance question and responses	Noise metric, (level range)
	NORAH[42,a]	3,502	Frankfurt, Germany 2012	Same as above	L_{night}, 2200–0600 hours (32.5–67.5 dB)
	NORAH[42,a]	3,505	Frankfurt, Germany 2013	Same as above	L_{night}, 2200–0600 hours (32.5–62.5 dB)
	NORAH[42,a]	5,519	Berlin, Germany 2012	Same as above	L_{night}, 2200–0600 hours (32.5–52.5 dB)
	NORAH[42,a]	2,939	Cologne–Bonn, Germany 2013	Same as above	L_{night}, 2200–0600 hours (32.5–67.5 dB)
	NORAH[42,a]	1,973	Stuttgart, Germany 2013	Same as above	L_{night}, 2200–0600 hours (32.5–52.5 dB)
	Schreckenberg et al.[54]	2,309	Germany	How much has aircraft noise in the last 12 months disturbed sleeping during the night? Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2200–0600 hours (37.5–57.5 dB)
Awakenings: noise not mentioned (total $N = 3,726$)	Rocha et al.[45,a]	309	Atlanta, Georgia, USA	How often did the following occur during the past month: You had trouble sleeping because you wake up in the middle of the night or early morning? Not during the past month, Less than once a week, Once or twice a week, Three or more times a week[b]	L_{night}, 2300–0700 hours (37.5–52.5 dB)
	Basner et al.[20,a]	39	Philadelphia, Pennsylvania, USA	During the past month, how often have you had trouble sleeping because you wake up in the middle of the night or early morning? Not during the past month, Less than once a week, Once or twice a week, Three or more times a week[b]	L_{night}, 2300–0700 hours (47.5–57.5 dB)
	Carugno et al.[35,a]	400	Bergamo, Italy	Frequent nocturnal awakening (last month)? No, Yes[b]	LVA, 2300–0600 hours (57.5–72.5 dB)
	Brink et al. (2003 study)[55]	1,450	Switzerland	How often do you have the following symptoms: Problems with sleeping through? Never, Rarely, Sometimes, Often, Very Often,[b] Always[b]	L_{night}, 2200–0600 hours (27.5–62.5 dB)
	Brink et al. (2001 study)[55]	1,528	Switzerland	Same as above	L_{night}, 2200–0600 hours (27.5–62.5 dB)
Falling asleep: noise not mentioned (total $N = 4,375$)	Smith et al.[21,a]	33	Atlanta, Georgia, USA	Please evaluate last night's sleep: falling asleep was Very easy (0) to Very difficult (10) (HSD 8,[b] 9,[b] 10[b])	L_{night}, 2300–0700 hours (37.5–57.5 dB)
	Nguyen et al.[32,a]	620	Hanoi, Vietnam	Do you have any trouble with your sleep? Difficult to fall asleep? Rarely/not at all, Once or twice a week, Three or more times per week[b]	L_{night}, 2200–0600 hours (32.5–62.5 dB)
	Rocha et al.[45,a]	309	Atlanta, Georgia, USA	How often did the following occur during the past month: You had trouble sleeping because you cannot get to sleep within 30 minutes? Not during the past month, Less than once a week, Once or twice a week, Three or more times a week[b]	L_{night}, 2300–0700 hours (37.5–52.5 dB)
	Basner et al.[20,a]	39	Philadelphia, Pennsylvania, USA	During the past month, how often have you had trouble sleeping because you cannot get to sleep within 30 minutes? Not during the past month, Less than once a week, Once or twice a week, Three or more times a week[b]	L_{night}, 2300–0700 hours (47.5–57.5 dB)
	Carugno et al.[35,a]	400	Bergamo, Italy	Long time to fall asleep (last month)? No, Yes[b]	LVA, 2300–0600 hours (57.5–72.5 dB)
	Brink et al. (2003 study)[55]	1,450	Switzerland	How often do you have the following symptoms: Problems falling asleep? Never, Rarely, Sometimes, Often, Very Often,[b] Always[b]	L_{night}, 2200–0600 hours (27.5–62.5 dB)
	Brink et al. (2001 study)[55]	1,528	Switzerland	Same as above	L_{night}, 2200–0600 hours (27.5–62.5 dB)
Sleep disturbance: noise not mentioned (total $N = 195$)	Brink[56]	195	Switzerland	During the last 4 weeks, have you suffered from any of the following disorders or health problems? Difficulty in sleeping or insomnia? Not at all, Somewhat, Very Much[b]	L_{night}, 2200–0600 hours (32.5–52.5 dB)

Note: HSD, highly sleep disturbed; L_{night}, nighttime noise; LVA, Livello di Valutazione del Aeroportuale; NORAH, Noise-Related Annoyance, Cognition and Health; WHO, World Health Organization.
[a]Studies not included in the WHO review.[19]
[b]Response alternatives designated as highly sleep disturbed.

Table 3. Studies on exposure to road traffic noise and self-reported sleep outcomes (adapted from the WHO review[19]).

Outcome	Study	N	Location	Disturbance question and responses	Noise metric (level range)
Awakenings: noise mentioned (total $N = 10{,}177$)	Bodin et al.[33]	2,438	Sweden	Do you experience any of the following because of road traffic noise? You wake up? Never, Sometimes, Often[b]	$L_{AEq,24h}$ (37.5–62.5 dB)
	Phan et al.[57] Shimoyama et al.[58]	1,454	Hanoi, Vietnam	How much are you disturbed by awakening during nighttime by road traffic? Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2200–0600 hours (62.5–77.5 dB)
	Phan et al.[57] Shimoyama et al.[58]	1,460	Ho Chi Minh City, Vietnam	Same as above	L_{night}, 2200–0600 hours (67.5–77.5 dB)
	Phan et al.[57] Shimoyama et al.[58]	479	Da Nang, Vietnam	Same as above	L_{night}, 2200–0600 hours (57.5–67.5 dB)
	Phan et al.[57] Shimoyama et al.[58]	680	Hue, Vietnam	Same as above	L_{night}, 2200–0600 hours (52.5–72.5 dB)
	Phan et al.[57] Shimoyama et al.[58]	777	Thai Nguyen, Vietnam	Same as above	L_{night}, 2200–0600 hours (52.5–67.5 dB)
	Sato et al.[59]	1,291	Gothenburg, Sweden	Does the road traffic noise cause the following conditions? Awakening? No, Little Disturbed, Rather Disturbed, Very Disturbed[b]	L_{night}, 2200–0700 hours (42.5–72.5 dB)
	Sato et al.[59]	819	Kumamoto, Japan	Same as above	L_{night}, 2200–0700 hours (47.5–77.5 dB)
	Sato et al.[59]	779	Sapporo, Japan	Same as above	L_{night}, 2200–0700 hours (52.5–67.5 dB)
Falling asleep: noise mentioned (total $N = 13{,}374$)	NORAH[42,a]	3,162	Frankfurt, Germany 2012	In the last 12 months road traffic noise has disturbed you when falling asleep? Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2200–0600 hours (32.5–72.5 dB)
	Bodin et al.[33]	2,444	Sweden	Do you experience any of the following because of road traffic noise? Difficulties falling asleep. Never, Sometimes, Often[b]	$L_{AEq,24h}$ (37.5–62.5 dB)
	Phan et al.[57] Shimoyama et al.[58]	1,471	Hanoi, Vietnam	How much are you disturbed in falling asleep by road traffic? Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2200–0600 hours (62.5–77.5 dB)
	Phan et al.[57] Shimoyama et al.[58]	1,458	Ho Chi Minh City, Vietnam	Same as above	L_{night}, 2200–0600 hours (67.5–77.5 dB)
	Phan et al.[57] Shimoyama et al.[58]	481	Da Nang, Vietnam	Same as above	L_{night}, 2200–0600 hours (57.5–67.5 dB)
	Phan et al.[57] Shimoyama et al.[58]	682	Hue, Vietnam	Same as above	L_{night}, 2200–0600 hours (52.5–72.5 dB)
	Phan et al.[57] Shimoyama et al.[58]	781	Thai Nguyen, Vietnam	Same as above	L_{night}, 2200–0600 hours (52.5–67.5 dB)
	Sato et al.[59]	1,302	Gothenburg, Sweden	Does the road traffic noise cause the following conditions? Difficulty to fall asleep? No, Little Disturbed, Rather Disturbed, Very Disturbed[b]	L_{night}, 2200–0700 hours (42.5–72.5 dB)
	Sato et al.[59]	814	Kumamoto, Japan	Same as above	L_{night}, 2200–0700 hours (47.5–77.5 dB)
	Sato et al.[59]	779	Sapporo, Japan	Same as above	L_{night}, 2200–0700 hours (52.5–67.5 dB)
Sleep disturbance: noise mentioned (total $N = 30{,}590$)	NORAH[42,a]	3,162	Frankfurt, Germany 2012	In the last 12 months road traffic noise has disturbed you when sleeping in the night? Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2200–0600 hours (32.5–72.5 dB)
	Brink et al.[46,a]	5,222	Switzerland	Thinking about the last twelve months at your home, during nighttime when you want to sleep, how much did road noise bother, disturb, or annoy you? Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2300–0700 hours (22.5–72.5 dB)
	Evandt et al.[37,a]	12,305	Norway	How disturbed have you been by noise during the night (falling asleep and waking up) from road noise in the last 12 months? Not at all, Slightly, Rather, Very,[b] Extremely[b]	L_{night}, 2300–0700 hours (37.5–67.5 dB)
	Brown et al.[60]	8,841	Hong Kong	How much is your sleep disturbed by road traffic noise? 11 point scale used from 0 (not disturbed at all) to 10 (extremely disturbed) (HSD 8,[b] 9,[b] 10[b])	L_{night} (42.5–67.5 dB)
	Hong et al.[61]	550	Korea	How much have you been disturbed in your sleep by road traffic noise at night when you are sleeping in your house over the last 12 months? 11 point scale used from 0	L_{night}, 2200–0700 hours (50.0–73.0 dB)

Table 3. (*Continued.*)

Outcome	Study	N	Location	Disturbance question and responses	Noise metric (level range)
				(not disturbed at all) to 10 (extremely disturbed) (HSD 8,[b] 9,[b] 10[b])	
	Ristovska et al.[62]	510	Macedonia	Do you think that your sleep was disturbed due to night-time noise or noise events during the night in the last twelve months and more? Not at all. Very little. Moderate, High[b], Very High[b]	L_{night}, 2300–0700 hours (42.5–62.5 dB)
Awakenings: noise not mentioned (total $N = 37{,}338$)	Martens et al.[34,a]	14,622	The Netherlands	How often during the past 4 weeks did you awaken during your sleep time and have trouble falling asleep again? Never, Seldom, Sometimes, Often,[b] Most of the time,[b] Always[b]	L_{den} (32.5–72.5 dB)
	Evandt et al.[37,a]	12,113	Norway	Have you noticed any of the following in the last 12 months? Repeatedly waking with difficulty falling back to sleep? No/rarely, Less than once a week, 1–2 times per week, 3–5 times per week,[b] Almost every night[b]	L_{night}, 2300–0700 hours, (37.5–67.5 dB)
	Bodin et al.[33]	2,519	Sweden	Do you wake up at night? Rarely/never, A few times per month, A few times a week, Almost every day[b]	$L_{AEq,24h}$ (37.5–62.5 dB)
	Frei et al.[63]	1,231	Switzerland	How often does it happen, that you wake up at night multiple times? Never, Rarely, Sometimes, Often[b]	L_{night}, 2200–0600 hours (27.5–62.5 dB)
	Halonen et al.[64]	6,853	Finland	How many times during the past 4 weeks have you had the following symptoms? Frequently waking up during the night. Never, 1 per month, 1 per week, 2–4 per week,[b] 5–6 per week,[b] nearly every night[b]	L_{night}, 2200–0700 hours (42.5–57.5 dB)
Falling asleep: noise not mentioned (total $N = 39{,}625$)	Bartels et al.[47]	2,188	Sweden	During the past 12 months, how often have you had problems falling asleep in the evening? Never/seldom, A few times per month, Once per week, Several times per week,[b] Every day[b]	L_{night}, 2200–0600 hours (22.5–72.5 dB)
	Martens et al.[34,a]	14,616	The Netherlands	How often during the past 4 weeks did you have trouble falling asleep? Never, Seldom, Sometimes, Often,[b] Most of the time,[b] Always[b]	L_{den} (32.5–72.5 dB)
	Evandt et al.[37,a]	12,276	Norway	Have you noticed any of the following in the last 12 months? Difficulty falling asleep? No/rarely, Less than once a week, 1–2 times per week, 3–5 times per week,[b] Almost every night[b]	L_{night}, 2300–0700 hours, (37.5–67.5 dB)
	Bodin et al.[33]	2,520	Sweden	Do you have problems falling asleep? Rarely/never, A few times per month, A few times a week, Almost every day[b]	$L_{AEq,24h}$ (37.5–62.5 dB)
	Frei et al.[63]	1,232	Switzerland	How often does it happen, that you cannot fall asleep well? Never, Rarely, Sometimes, Often[b]	L_{night}, 2200–0600 hours (27.5–62.5 dB)
	Halonen et al.[64]	6,793	Finland	How many times during the past 4 weeks have you had the following symptoms? Difficulty falling asleep? Never, 1 per month, 1 per week, 2–4 per week,[b] 5–6 per week,[b] Nearly every night[b]	L_{night}, 2200–0700 hours (42.5–57.5 dB)
Sleep disturbance: noise not mentioned (total $N = 24{,}093$)	Martens et al.[34,a]	14,619	The Netherlands	How often during the past 4 weeks did you feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc.) while sleeping? Never, Seldom, Sometimes, Often,[b] Most of the time,[b] Always[b]	L_{den} (32.5–72.5 dB)
	Frei et al.[63]	1,229	Switzerland	How often does it happen that your sleep is restless? Never, Rarely, Sometimes, Often[b]	L_{night}, 2200–0600 hours (27.5–62.5 dB)
	Brink et al.[56]	8,245	Switzerland	During the last 4 weeks, have you suffered from any of the following disorders or health problems? Difficulty in sleeping, or insomnia? Not at all. Somewhat, Very Much[b]	L_{night}, 2200–0600 hours (32.5–77.5 dB)

Note: HSD, highly sleep disturbed; $L_{AEq,24h}$, air and road traffic noise at 24-h average levels; L_{den}, day-evening-night level; L_{night}, nighttime noise; NORAH, Noise-Related Annoyance, Cognition and Health; WHO, World Health Organization.
[a]Studies not included in the WHO review.[19]
[b]Response alternatives designated as highly sleep disturbed.

Table 4. Studies on exposure to railway noise and self-reported sleep outcomes (adapted from the WHO review[19]).

Outcome	Study	N	Location	Disturbance question and responses	Noise metric (level range)
Awakenings: noise mentioned (total $N = 5{,}311$)	Bodin et al.[33]	2,344	Sweden	Do you experience any of the following because of railway noise? You wake up? Never, Sometimes, Often[b]	$L_{AEq,24h}$ (37.5–62.5 dB)
	Sato et al.[65]	1,418	Hokkaido, Japan	How much are you disturbed by awakening during nighttime by train passing? Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2200–0700 hours (27.5–62.5 dB)
		1,549	Kyushu, Japan		L_{night}, 2200–0700 hours (27.5–72.5)
Falling asleep: noise mentioned (total $N = 9{,}786$)	NORAH[42,a]	3,266	Frankfurt, Germany 2012	In the last 12 months railway noise has disturbed you when falling asleep? Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2200–0600 hours (27.5–82.5 dB)
	Bodin et al.[33]	2,342	Sweden	Do you experience any of the following because of railway noise? Difficulties falling asleep? Never, Sometimes, Often[b]	$L_{AEq,24h}$ (37.5–62.5 dB)
	Schreckenberg[66]	1,198	Germany	To what extent have the following outcomes of railway noise occurred in the past 12 months? Railway noise disturbs when falling asleep. Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2200–0600 hours (42.5–82.5 dB)
	Sato et al.[65]	1,418	Hokkaido, Japan	How much are you disturbed in falling asleep by train passing? Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2200–0700 hours (27.5–62.5 dB)
		1,562	Kyushu, Japan		L_{night}, 2200–0700 hours (27.5–72.5 dB)
Sleep disturbance: noise mentioned (total $N = 21{,}094$)	NORAH[42,a]	3,266	Frankfurt, Germany 2012	In the last 12 months railway noise has disturbed you when sleeping in the night? Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2200–0600 hours (27.5–82.5 dB)
	Brink et al.[46,a]	3,543	Switzerland	Thinking about the last twelve months at your home, during nighttime when you want to sleep, how much did railway noise bother, disturb, or annoy you? Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2300–0700 hours (22.5–77.5 dB)
	Evandt et al.[37,a]	12,476	Norway	How disturbed have you been by noise during the night (falling asleep and waking up) from rail noise in the last 12 months? Not at all, Slightly, Rather, Very,[b] Extremely[b]	L_{night}, 2300–0700 hours, (37.5–67.5 dB)
	Schreckenberg[66]	1,199	Germany	To what extent have the following outcomes of railway noise occurred in the past 12 months? Railway disturbs when sleeping during the night. Not at all, Slightly, Moderately, Very,[b] Extremely[b]	L_{night}, 2200–0600 hours (42.5–82.5 dB)
	Hong et al.[61]	610	Korea	How much have you been disturbed in your sleep by railway noise at night when you are sleeping in your house over the last 12 months? 11 point scale used from 0 (not disturbed at all) to 10 (extremely disturbed) (HSD 8,[b] 9,[b] 10[b])	L_{night}, 2200–0700 hours (47.1–70 dB)
Awakenings: noise not mentioned (total $N = 16{,}383$)	Evandt et al.[37,a]	12,577	Norway	Have you noticed any of the following in the last 12 months? Repeatedly waking with difficulty falling back to sleep? No/rarely, Less than once a week, 1–2 times per week, 3–5 times per week,[b] Almost every night[b]	L_{night}, 2300–0700 hours, (37.5–67.5 dB)
	Bodin et al.[33]	2,575	Sweden	Do you wake up at night? Rarely/never, A few times per month, A few times a week, Almost every day[b]	$L_{AEq,24h}$ (37.5–62.5 dB)
	Frei et al.[63]	1,231	Switzerland	How often does it happen, that you wake up at night multiple times? Never, Rarely, Sometimes, Often[b]	L_{night}, 2200–0600 hours (27.5–57.5 dB)
Falling asleep: noise not mentioned (total $N = 16{,}553$)	Evandt et al.[37,a]	12,745	Norway	Have you noticed any of the following in the last 12 months? Difficulty falling asleep? No/rarely, Less than once a week, 1–2 times per week, 3–5 times per week,[b] Almost every night[b]	L_{night}, 2300–0700 hours, (37.5–67.5 dB)
	Bodin et al.[33]	2,576	Sweden	Do you have problems falling asleep? Rarely/never, A few times per month, A few times a week, Almost every day[b]	$L_{AEq,24h}$ (37.5–62.5 dB)
	Frei et al.[63]	1,232	Switzerland	How often does it happen, that you cannot fall asleep well? Never, Rarely, Sometimes, Often[b]	L_{night}, 2200–0600 hours (27.5–57.5 dB)
Sleep disturbance: noise not mentioned (total $N = 5{,}914$)	Frei et al.[63]	1,229	Switzerland	How often does it happen that your sleep is restless? Never, Rarely, Sometimes, Often[b]	L_{night}, 2200–0600 hours (27.5–57.5 dB)
	Brink et al.[56]	4,685	Switzerland	During the last 4 weeks, have you suffered from any of the following disorders or health problems? Difficulty in sleeping, or insomnia? Not at all, Somewhat, Very Much[b]	L_{night}, 2200–0600 hours (32.5–77.5 dB)

Note: HSD, highly sleep disturbed; $L_{AEq,24h}$, air and road traffic noise at 24-h average levels; L_{night}, nighttime noise; NORAH, Noise-Related Annoyance, Cognition and Health; WHO, World Health Organization.
[a]Studies not included in the WHO review.[19]
[b]Response alternatives designated as highly sleep disturbed.

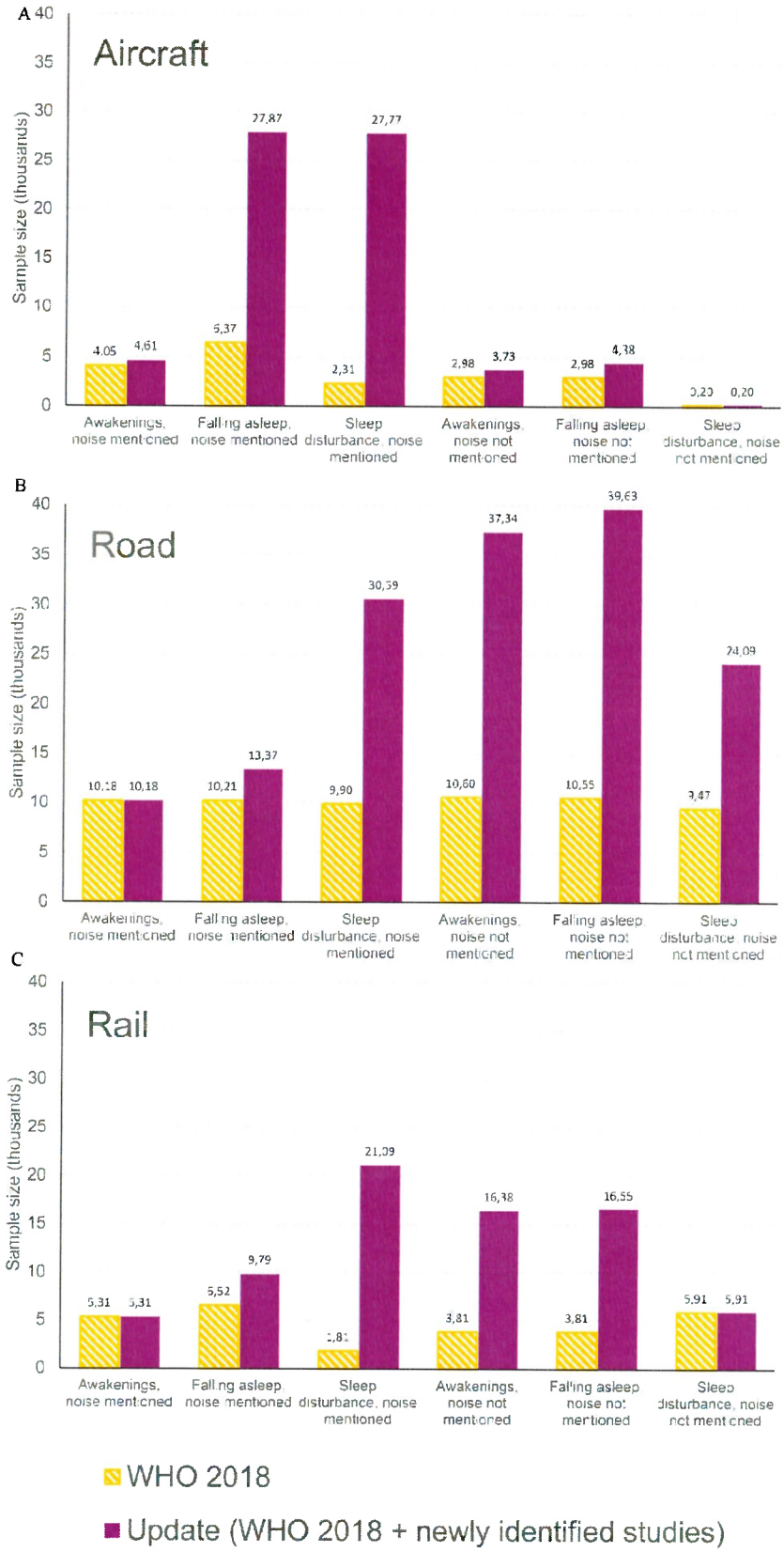


Figure 2. Effective sample sizes for (A) aircraft, (B) road, and (C) rail for each sleep disturbance question in the present updated analysis, determined from the original WHO analysis plus the 11 newly included studies, compared with sample sizes from the WHO 2018 review only.[19] Note: WHO, World Health Organization.

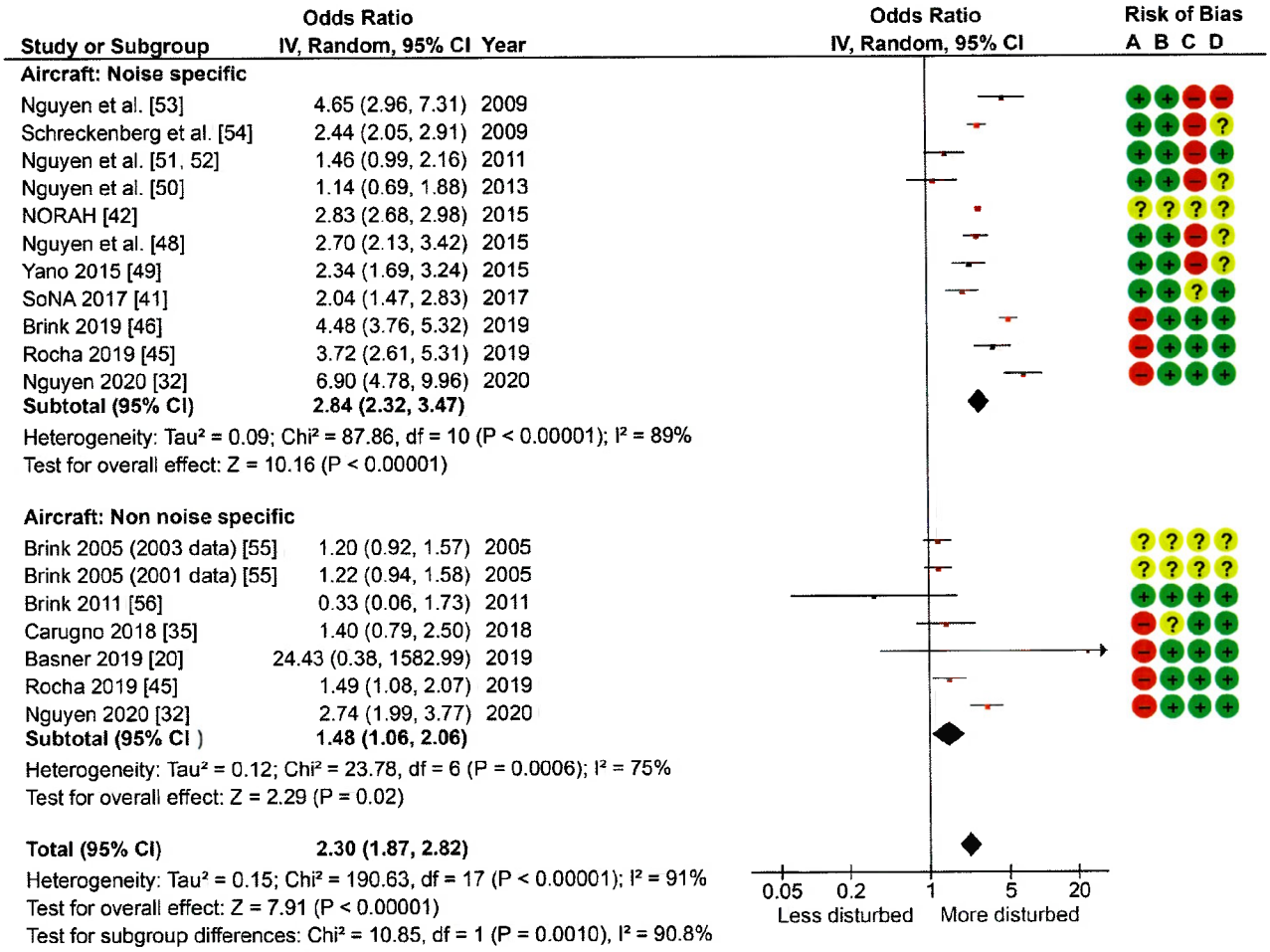


Figure 3. Forest plot for the odds of being highly sleep disturbed by aircraft noise per 10-dB increase in L_{night} (combined estimate derived from all relevant outcomes within studies). Subgroups are presented for questions that mentioned noise as the source of the disturbance, and questions that did not specify noise as the source of the disturbance. Risk of bias: A: selection bias; B: exposure assessment; C: confounding; D: reporting bias. Green (+) denotes low risk of bias, red (–) denotes high risk of bias, yellow (?) denotes unclear risk of bias. Plots were generated using an inverse-variance (IV) random effects method across the full noise range for each individual study (not restricted to 40–65 dB L_{night}). Note: CI, confidence interval; df, degrees of freedom; L_{night}, nighttime noise; NORAH, Noise-Related Annoyance, Cognition and Health.

studies are given in Figure S1. For all three traffic modes, our updated analysis includes a substantially higher number of respondents for all self-reported disturbance questions.

Sleep Disturbance by Noise: Individual Studies

ORs for the probability of being highly sleep disturbed by noise for each study are shown in Figure 3 (aircraft), Figure 4 (road traffic), and Figure 5 (railway). Also shown is the risk of bias assessment for each study (Table S4 for the rationale for each judgment). With a 10-dB increase in L_{night}, there was a statistically significant probability of being sleep disturbed by noise for all three traffic modes. This increased probability was independent of whether noise was specifically mentioned in the sleep question. There were significant differences between the subgroups for each traffic mode, and the ORs were lower in studies that did not specifically mention noise. There was considerable heterogeneity ($I^2 \geq 75\%$) for all three traffic modes when the sleep question mentioned noise. There was substantial heterogeneity ($50\% \leq I^2 \leq 90\%$) between studies of aircraft and road traffic when the sleep question did not specifically mention noise. The heterogeneity between studies of railway noise was deemed unimportant ($I^2 \leq 40\%$) when the sleep question did not specifically mention noise.

Sleep Disturbance by Noise: Overall Analysis

The ORs for the probability of being highly sleep disturbed by nighttime noise, calculated using data from all studies and restricted to 40–65 dB L_{night}, are presented in Table 5. When the question mentioned noise as the source of disturbance, there was a higher probability of being significantly disturbed by noise for all three outcomes, as well as for the combined estimate. When the question did not mention noise, significant relationships were observed only for aircraft and road noise, and for only some of the sleep disturbance outcomes. A substantial proportion of studies into road and railway noise were judged as having a high risk of exposure assessment bias when the question mentioned noise. We decided post hoc to perform a sensitivity analysis for these traffic types, to elucidate the influence of these risks of bias on sleep disturbance. There was a greater probability of being highly sleep disturbed by noise in studies with a low risk of exposure assessment bias compared with studies with a high risk of exposure assessment bias (Table S5).

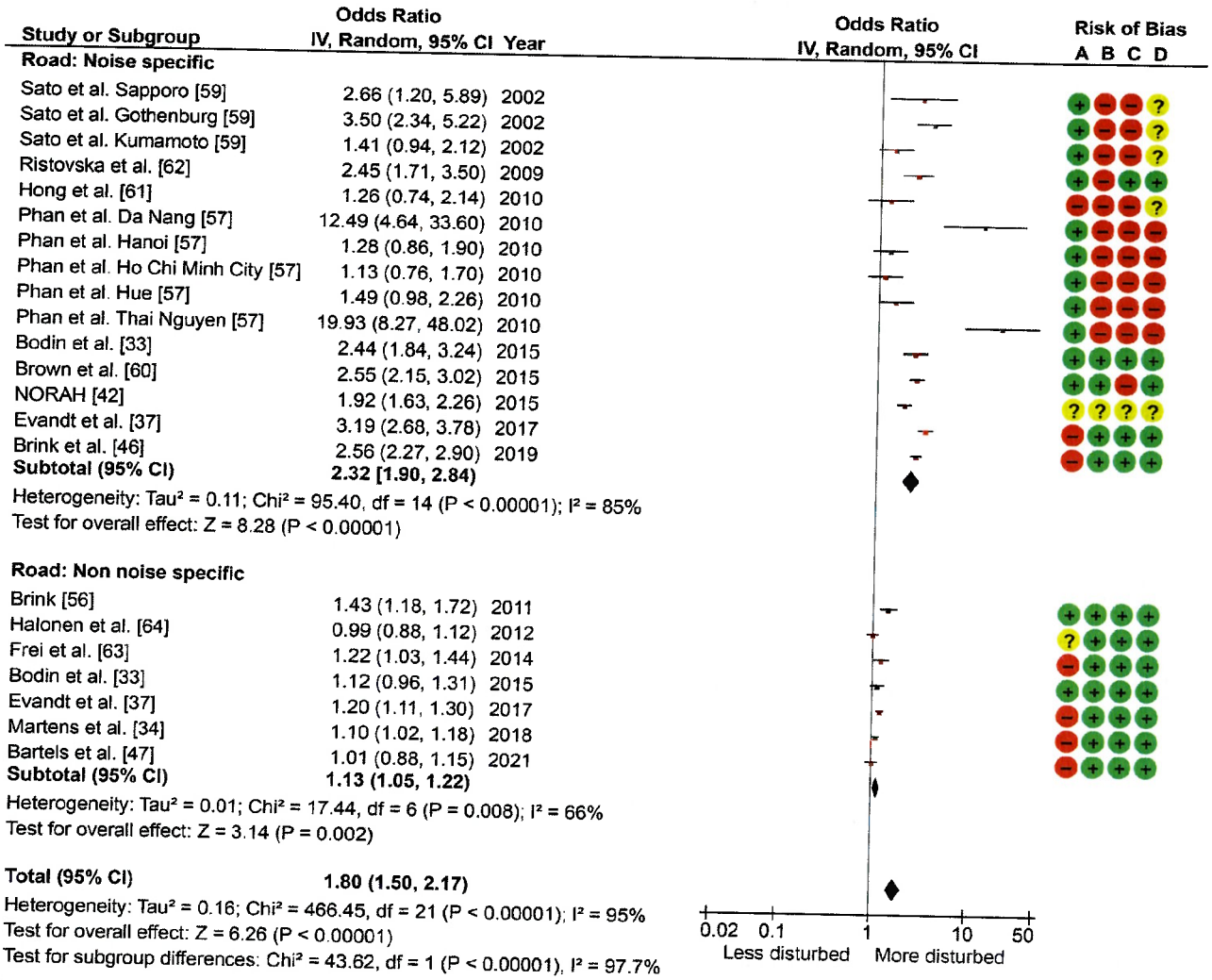


Figure 4. Forest plot for the odds of being highly sleep disturbed by road noise per 10-dB increase in L_{night} (combined estimate derived from all relevant outcomes within studies). Subgroups are presented for questions that mentioned noise as the source of the disturbance, and questions that did not specify noise as the source of the disturbance. Risk of bias: A: selection bias; B: exposure assessment; C: confounding; D: reporting bias. Green (+) denotes low risk of bias, red (–) denotes high risk of bias, yellow (?) denotes unclear risk of bias. Plots were generated using an inverse-variance (IV) random effects method across the full noise range for each individual study (not restricted to 40–65 dB L_{night}). Note: CI, confidence interval; df, degrees of freedom; L_{night}, nighttime noise; NORAH, Noise-Related Annoyance, Cognition and Health.

The ORs for the probability of being highly sleep disturbed, stratified by studies performed in Europe and outside of Europe, are given in Table S6. Analyses were restricted to aircraft, road, and railway traffic when the question mentioned noise, plus aircraft traffic when noise was not specifically mentioned, because these were the outcomes where sleep disturbance data were available for both locations. Non-European study respondents were more highly sleep disturbed by railway traffic when noise was mentioned in the question and by aircraft traffic when noise was not specifically mentioned. Non-Europeans were also less disturbed by road traffic when noise was mentioned. However, none of these effects were significant.

Exposure–Response Curves: Questions Specifically Mentioning Noise

The exposure–response curves for the probability of being highly sleep disturbed, derived using data from questions that specifically mentioned noise, are given in Figure 6. Second-order polynomial equations for each curve are given in Table S7. Disturbance was substantially higher for aircraft noise for all three disturbance questions than for road or railway noise of the same level. Disturbance was similar for road and rail noise at low noise levels, and it was slightly higher for railway noise than road noise at higher noise levels.

We compared the updated exposure–response curves to curves derived using only the 11 new studies published since the WHO review[19] (Figure 7). This was done for the combined estimate only, given that there was a limited sample size for certain sleep questions in these recent studies. For aircraft noise, the recent studies indicated a higher probability of being highly sleep disturbed compared with the analysis incorporating all available data. For road traffic noise, the point estimates were slightly higher at the highest noise levels in the recent studies compared with the overall analysis (2.6% higher at 65 dB L_{night}). For railway noise, the recent studies were essentially identical to the overall analysis.

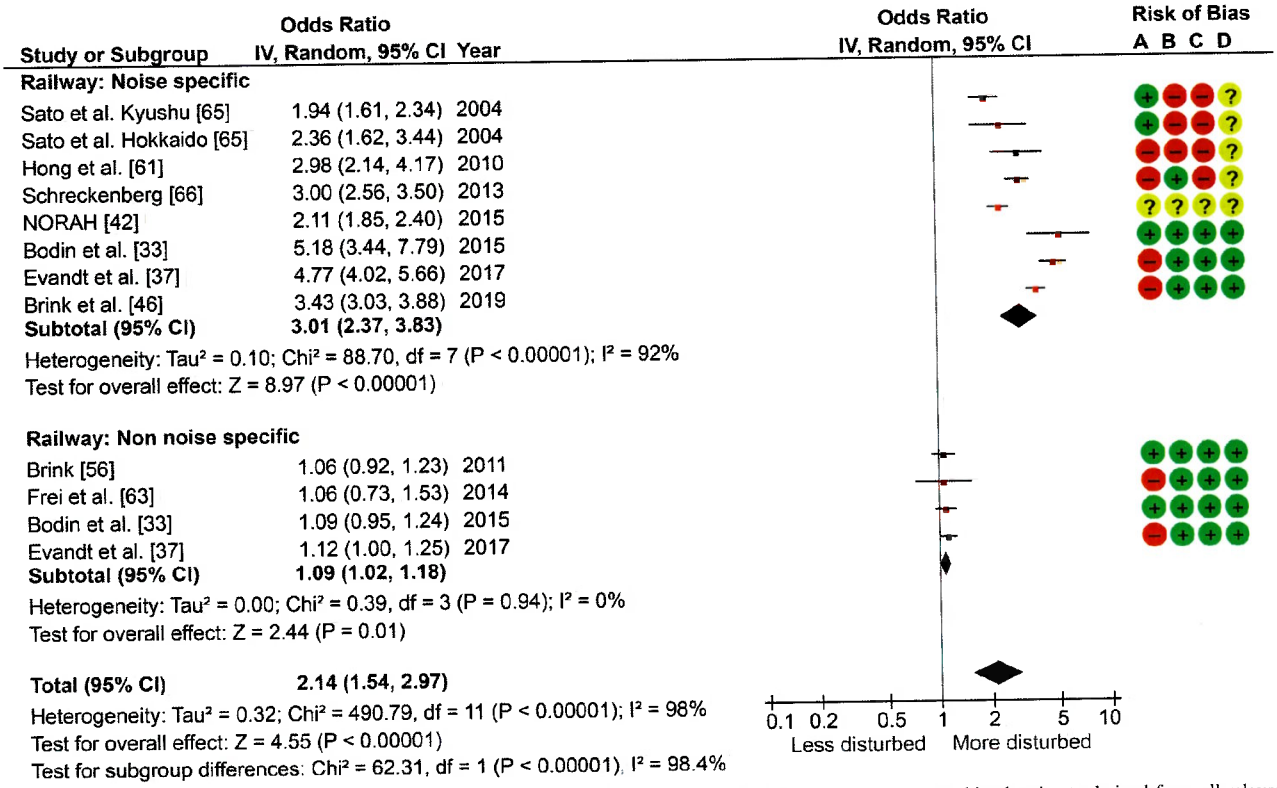


Figure 5. Forest plot for the odds of being highly sleep disturbed by railway noise per 10-dB increase in L_{night} (combined estimate derived from all relevant outcomes within studies). Subgroups are presented for questions that mentioned noise as the source of the disturbance, and questions that did not specify noise as the source of the disturbance. Risk of bias: A: selection bias; B: exposure assessment; C: confounding; D: reporting bias. Green (+) denotes low risk of bias, red (−) denotes high risk of bias, yellow (?) denotes unclear risk of bias. Plots were generated using an inverse-variance (IV) random effects method across the full noise range for each individual study (not restricted to 40–65 dB L_{night}). Note: CI, confidence interval; L_{night}, nighttime noise; NORAH, Noise-Related Annoyance, Cognition and Health.

The exposure–response curves calculated in the original WHO review [19] are given in Figure 6. Relationships for the sleep disturbance question were not calculated in the WHO review due to an insufficient number of studies at the time. Point estimates for aircraft noise are generally slightly higher in the present analyses compared with the previous relationships, particularly at higher noise levels, although they still lie within the 95% CIs of the WHO review. Point estimates for the falling asleep and combined estimate outcomes are almost identical for road and rail traffic in the present analysis compared with the WHO review. For each disturbance question and traffic mode, all of the previous curves lie within the 95% CIs of the updated analyses. As expected, given that no additional studies were included for awakenings by aircraft or road traffic, exposure–response curves for these outcomes were identical to curves in the WHO review.

Table 5. Odds ratios per 10-dB increase in L_{night} for the percent highly sleep disturbed by aircraft, road, and railway traffic noise.

		Noise mentioned as source of disturbance			Noise not mentioned as source of disturbance		
Noise source	Outcome	Studies (n)[a]	Sample size (n)[a]	OR per 10 dB (95% CI)	Studies (n)[a]	Sample size (n)[a]	OR per 10 dB (95% CI)
Aircraft noise	Awakenings	6	4,137	2.34 (1.87, 2.93)	5	2,571	1.11 (0.81, 1.53)
	Falling asleep	8	17,107	2.09 (1.91, 2.28)	7	3,120	1.67 (1.27, 2.19)
	Sleep disturbance	5	15,345	2.28 (2.03, 2.56)	1	153	1.22 (0.08, 18.20)
	Combined estimate	11	19,488	2.18 (2.01, 2.36)	8	3,275	1.52 (1.20, 1.93)
Road noise	Awakenings	8	5,355	1.75 (1.24, 2.47)	5	29,358	1.10 (1.01, 1.20)
	Falling asleep	9	7,754	2.31 (1.85, 2.89)	6	31,136	1.15 (1.08, 1.23)
	Sleep disturbance	6	26,372	2.57 (2.26, 2.93)	3	18,052	1.15 (0.93, 1.43)
	Combined estimate	14	31,738	2.52 (2.28, 2.79)	7	38,380	1.14 (1.08, 1.21)
Railway noise	Awakenings	3	3,576	2.54 (1.49, 4.33)	3	3,197	1.09 (0.78, 1.53)
	Falling asleep	5	6,730	2.70 (2.14, 3.42)	3	3,219	1.27 (0.84, 1.90)
	Sleep disturbance	5	7,262	3.35 (2.75, 4.09)	2	1,168	1.27 (0.11, 15.15)
	Combined estimate	8	10,846	2.97 (2.57, 3.43)	4	4,326	1.17 (0.91, 1.49)

Note: ORs were calculated in logistic regression models with L_{night} included as the only fixed effect and study included as a random effect, restricted to the noise exposure range 40–65 dB L_{night}. Models were run separately for each traffic mode and for sleep questionnaire outcomes that did or did not mention noise. The combined estimate was calculated using average responses of the awakening, falling asleep, and sleep disturbance questions within studies. CI, confidence interval; L_{night}, nighttime noise; OR, odds ratio.
[a]In the L_{night} range 40–65 dB for which ORs were calculated.

Exposure–Response Curves: Questions Not Specifically Mentioning Noise

The exposure–response curves for the probability of being highly sleep disturbed, derived using data from general sleep questions that did not specifically mention noise, are given in Figure 8. Second-order polynomial equations for each curve are given in Table S7. With increasing L_{night}, there was a small increase in disturbance for all questions, although the gradient of the exposure–response curves was generally smaller compared with questions that mentioned noise (Figure 6). The differences between the three traffic modes were also less clear compared with questions mentioning noise (Figure 6).

Quality of Evidence for Being Highly Sleep Disturbed by Noise

Funnel plots of the combined estimate for each traffic mode are given in Figure S2. The plots were approximately symmetrical, indicating a low likelihood of publication bias.

The GRADE profile for the assessment of the quality of evidence across studies is given in Table 6. In the assessment, we deemed that for the majority of studies to be considered high quality (study limitations domain), there should be a low risk of selection bias and also a low risk of exposure assessment bias. If there was a high risk for one or both of these biases in the majority of studies, then overall study quality was deemed low. The overall quality of evidence for nighttime noise from aircraft, road, and railway traffic was rated as moderate when the question mentioned noise. When the question did not mention noise, the quality of evidence was low for aircraft and road traffic noise and very low for railway noise.

Discussion

Noise-Specific Sleep Disturbance

In an update to the latest WHO evidence review and meta-analysis for the effects of traffic noise on self-reported sleep disturbance,[19] we found significant exposure–response relationships for being highly sleep disturbed by nighttime aircraft, road, and railway traffic when the sleep questions explicitly mentioned noise. With increasing nighttime noise levels, and for all three traffic modes, there were increased probabilities of reporting awakenings, having difficulties falling asleep, or having disrupted or disturbed sleep. When the sleep disturbance outcomes were combined for each traffic mode separately, the resulting exposure–response curves for road and railway noise were very similar to those calculated in the WHO review (Figure 6). The similarity in the exposure–response curves improves confidence in the earlier estimates, which informed recent WHO recommendations for nighttime noise from road (45 dB L_{night}) and rail (44 dB L_{night}).[15] For aircraft noise, our updated estimates show a higher probability of being highly sleep disturbed at high L_{night} levels. At 40 dB L_{night}, however, which is the WHO recommendation for nighttime aircraft noise,[15] our updated estimates closely match the point estimates from the previous evidence review.[19]

The ORs for aircraft noise were lower than for both road and railway noise. This is a consequence of the properties of ORs as a relative measure, given that a much higher proportion of people were sleep disturbed by aircraft noise at low reference noise levels. The exposure–response curves show that aircraft noise was in fact more disturbing than road or rail noise of the same level. This finding, although also seen in the original WHO review,[19] is superficially surprising in light of experimental studies showing that aircraft noise is less disruptive to physiological sleep than road or rail traffic.[67] The reasons for higher self-reported disturbance by aircraft are unclear but could result from the timing of aircraft noise events. Nighttime noise levels from aircraft are typically dominated by passenger plane takeoffs and landings that occur at the very start and the very end of the night period (2300–0700 hours). The early night is a period when many people are trying to fall asleep, and the end of the night is a period when people may be awakened by noise more easily, or have greater difficulty falling back asleep after awakenings, because sleep pressure has been dissipated over the preceding night. Noise around these times could therefore have a greater impact on self-reported disturbance than at other times of night. Such an explanation is supported by the higher disturbance for specific questions on awakenings and difficulties falling asleep owing to aircraft noise.

It is also possible that the higher disturbance by aircraft is a result of exposure misclassification. In most studies, noise was assessed at the most exposed façade, and the exposure levels specifically in the bedroom are not known. Noise levels in the bedroom for road and railway traffic are most likely lower, on average, than at the most exposed façade, because bedrooms may be located on quieter sides of the building. There is probably less exposure misclassification for aircraft noise, especially for homes that lie under flight paths, given that the positions of aircraft as noise sources are more dynamic relative to the home. Finally, it is possible that particular characteristics of air traffic are somehow more disturbing than road or rail noise of the same level. Aircraft noise events have a much longer duration than the other traffic modes, and so there are longer windows to become cognizant of the noise and attribute it as a source of sleep disturbance. However, each of these explanations cannot be thoroughly explored without additional temporal, spatial, and acoustical data for the noise sources.

Non-Noise-Specific Sleep Disturbance

The probability of being highly sleep disturbed was less clear when studies used general sleep questions that did not mention noise. For those sleep outcomes, all ORs were in the same direction and >1.0, suggesting potentially increasing disturbance with noise level. However, the effect sizes were smaller compared with noise-specific questions, and they were significant for only a minority of outcomes (5 of 12) assessed across all traffic modes.

Differences in sleep disturbance between studies employing general sleep questions and studies that specifically mention noise could result from heterogeneity between studies generally, which is discussed in detail later. When a question mentions a particular traffic source, a respondent may be better able to correctly attribute noise-induced sleep disturbance to that source, which could also explain the higher effect sizes in studies mentioning noise. Misattributing noise as the reason for an endogenous sleep is also possible, for instance, if respondents awaken spontaneously in the absence of noise, and a noise event that is later recalled coincidentally occurs during the awakening bout. A further important effect modifier could be noise sensitivity. Because noise-sensitive individuals may be more likely to report sleep disturbance than their less-sensitive counterparts,[68–70] they might rate themselves as more sleep disturbed to questions explicitly mentioning noise.

Risk of Bias, Quality of Evidence, and Study Heterogeneity

Most newly included studies were rated as having a high risk of selection bias. In most cases, this was due to response rates being <50%. Low survey response rates in public health research are becoming increasingly common,[71] something that can increase

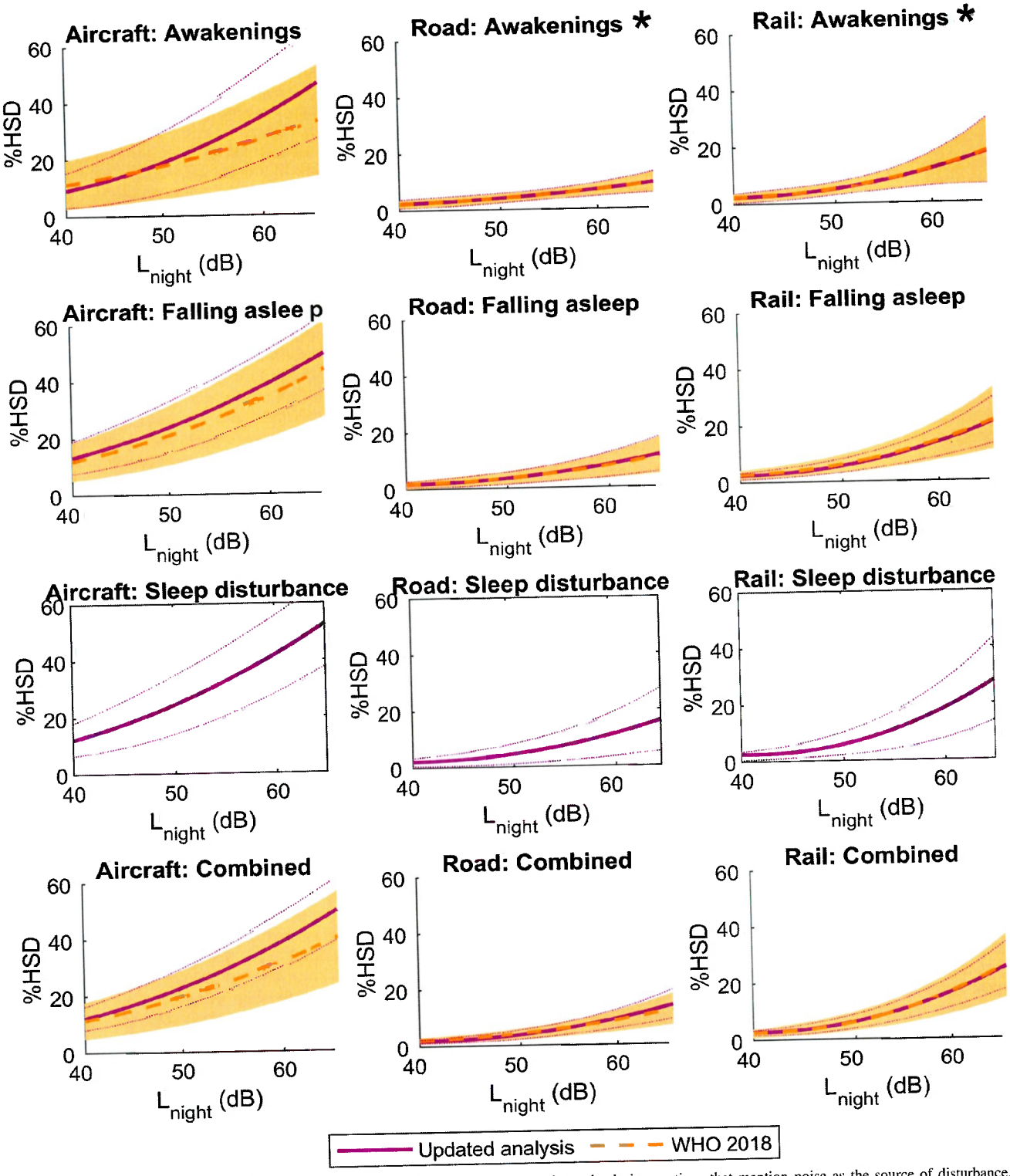


Figure 6. Probability of being highly sleep disturbed (%HSD) by nighttime noise, determined via questions that mention noise as the source of disturbance, stratified by disturbance question and traffic mode. Exposure–response relationships were derived using all available data, from the original WHO review[19] and the 11 newly identified studies. Results of the present updated analysis (solid purple lines with dotted 95% CIs) are compared against results of the 2018 WHO review[19] (dashed orange lines with shaded 95% CIs). Relationships for the sleep disturbance questions were not calculated previously. Asterisks (*) indicate sleep outcomes for which no new studies have been published since the WHO review. Parameter estimates were calculated in logistic regression models with L_{night} included as the only fixed effect and study included as a random effect, restricted to the noise exposure range 40–65 dB L_{night}. Models were run separately for each traffic mode and disturbance question. The combined estimate was calculated using average responses of the awakening, falling asleep, and sleep disturbance questions within studies. Note: CI, confidence interval; L_{night}, nighttime noise; WHO, World Health Organization.

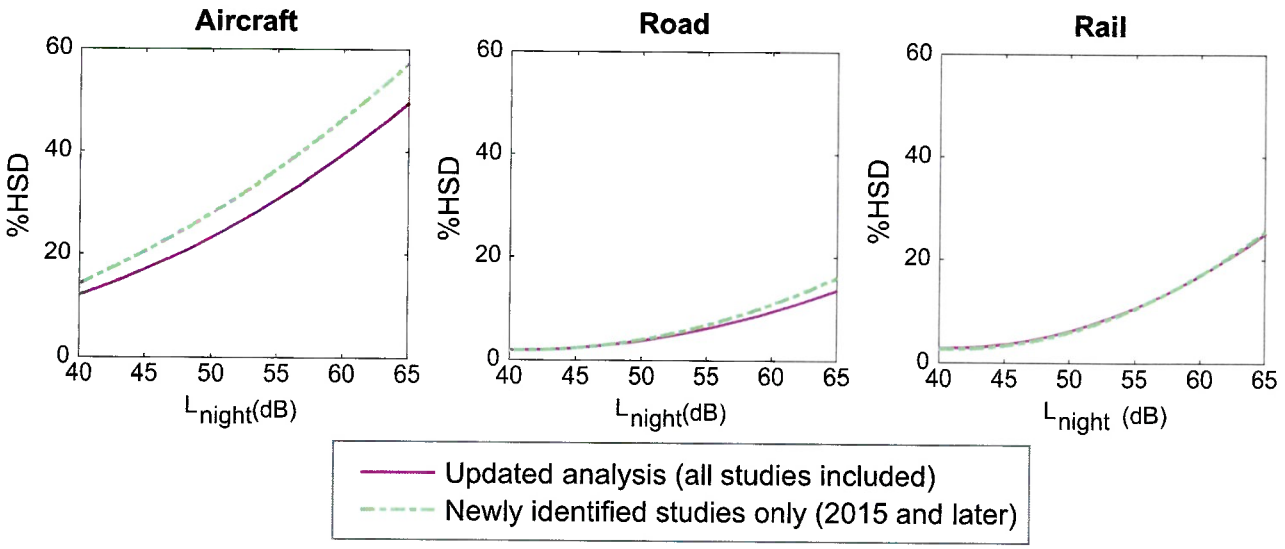


Figure 7. Exposure–response relationships for the probability of being highly sleep disturbed (%HSD) by nighttime noise for questions that mention noise. Curves are shown for the updated analysis that includes all available data (solid purple lines), and for analysis including only newly identified studies published after the WHO review[19] (dashed green lines). Data are calculated as the combined response using average responses of the awakening, falling asleep, and sleep disturbance questions within studies, determined as the within-study average of disturbance questions that explicitly mentioned noise as the source of sleep disturbance. Parameter estimates were calculated in logistic regression models with L_{night} included as the only fixed effect and study included as a random effect, restricted to the noise exposure range 40–65 dB L_{night}. Models were run separately for each traffic mode. Note: L_{night}, nighttime noise; WHO, World Health Organization.

the risk of nonresponse bias.[72] However, nonresponse bias can occur in studies with both low and high response rates.[73] More important than response rates is that the survey responses are representative of the target population sampled,[74] and surveys can still be representative even with lower response rates. Lacking nonresponse analyses, we cannot be certain of the representativeness of the exposure–response relationships, although the high risk of selection bias in the included studies does not necessarily mean that the sleep outcomes are unrepresentative of the overall population exposed to noise. Further studies with increased response rates would decrease the likelihood of nonresponse bias.

Sensitivity analysis revealed that sleep disturbance was lower in studies with a high risk of exposure assessment bias. One possible explanation is that road and railway noise exposure in the bedroom was overestimated in studies judged to have a high risk of bias. This would, in effect, shift the exposure–response relationships to the right in these studies. Alternatively, differences in sleep disturbance could be confounded by the fact that all studies with high risk of exposure assessment bias were published between 2002 and 2010, whereas the low risk of bias studies were from published more recently, between 2013 and 2021. It is plausible that the higher probability of high sleep disturbance in newer studies is attributable to nonacoustical factors, such as changes in attitudes to noise. Temporal changes in self-reported response would align with observed trends for increasing annoyance by a given level of traffic noise, although these trends have been observed predominantly for aircraft rather than road or rail traffic.[75] There have also been changes in the acoustical character of noise, with newer vehicles being typically quieter but with noise occurring more often as traffic flows increase, which may negatively influence perceived sleep disturbance.

The overall quality of evidence differed between studies where sleep disturbance questions did or did not mention noise. The assessment of a moderate quality of evidence for sleep disturbance when the question mentioned noise agrees with the assessment in the WHO review.[19] When the question did not specifically mention noise, we graded the quality of evidence for exposure to railway noise as very low, again agreeing with the WHO review, and the quality of evidence as low for aircraft and road traffic noise, which is one level higher than the very low quality assessment in the WHO review. The reason for the upgrade for aircraft and road noise was due to the statistically significant trends for awakenings (road only), falling asleep, and the combined estimates, that were not found previously. Since the previous review, three major cross-sectional studies involving road traffic noise exposure, with a combined sample size of ~29,000 respondents, were published.[34,37,47] The exposure–response relationships for non-noise-dependent disturbance are thus more representative, and with substantially greater power, than previously found.

There was substantial heterogeneity between studies for all outcomes except studies of railway noise that employed general sleep questionnaires. The heterogeneity could result from variations in the specific phrasing of the sleep disturbance question across studies, even when ostensibly measuring the same outcome. There was also a diverse range of response scales, with 11-point numerical and 3-, 4-, or 5-point verbal scales used to assess sleep disturbance, further diversified by assessing either the severity or the frequency of disturbance. These questions were administered in 14 nations, hence, there may be linguistic differences in the interpretation of certain phrases, as well as cultural differences in attitudes to sleep or noise, as well as contextual differences generally across specific studies. Questions also differed in the reference time frame for sleep disturbance, varying from the last 12 months to the last 4 wk to referencing specific noise events or no time frame at all. Finally, self-reported response to noise can be modified by contextual factors separate from noise level alone, including lifestyle, access to green space, access to quiet areas, social interaction, recreational activities, and local economy of the neighbourhood.[76] One or several of these factors could have contributed to study heterogeneity within specific sleep outcomes, across studies of different traffic modes, or across studies that used either general sleep questions or noise-specific disturbance questions.

Study Location

The majority of new studies originated from Europe. All newly included studies of road[34,37,42,46,47] and railway[37,42,46] noise were

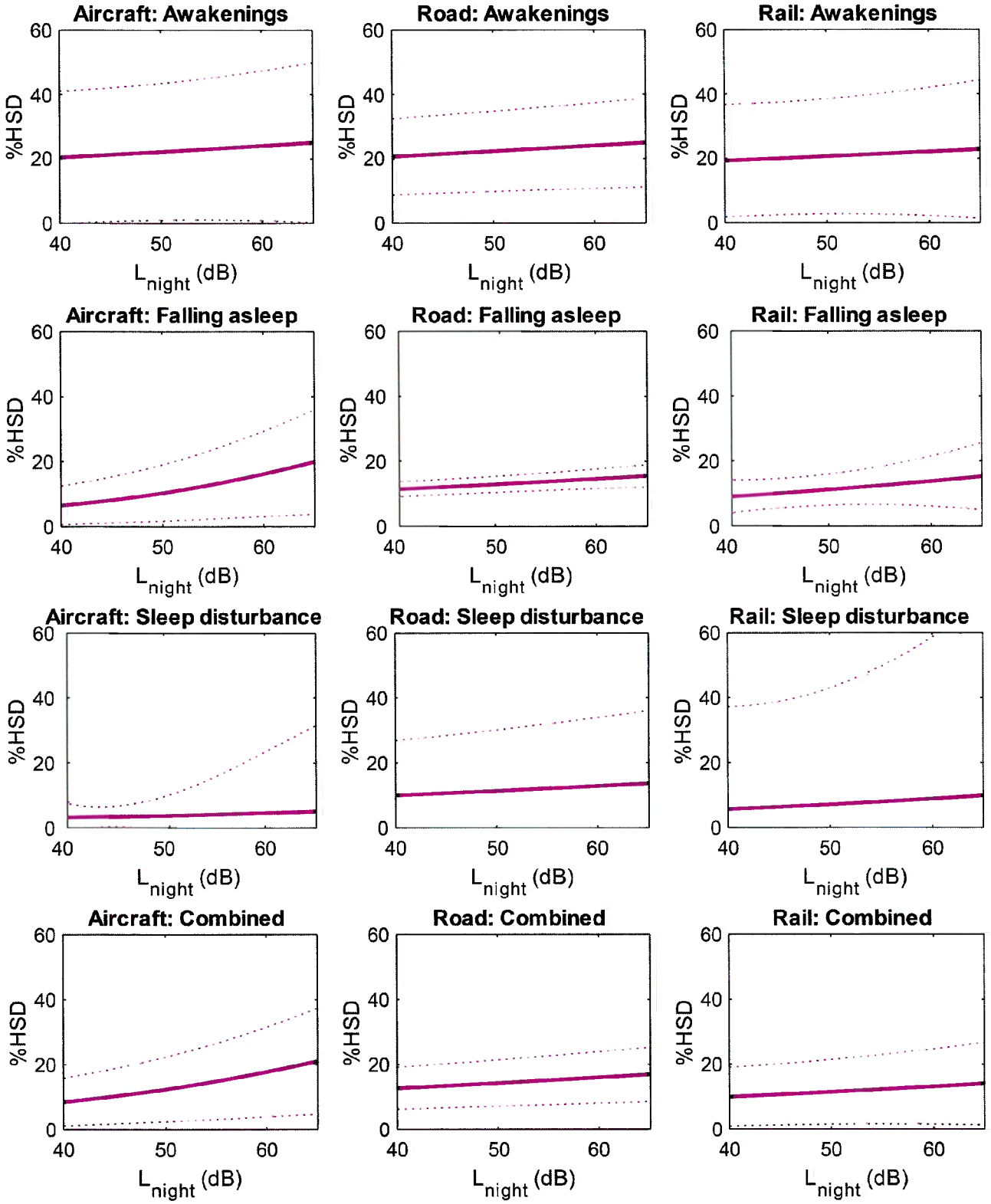


Figure 8. Probability of being highly sleep disturbed (%HSD) by nighttime noise, determined via questions that did not specifically mention noise as the source of disturbance, stratified by disturbance question and traffic mode. Exposure–response relationships were derived using all available data, from the original WHO review[19] and the 11 newly identified studies. Dotted lines indicate 95% CIs. Parameter estimates were calculated in logistic regression models with L_{night} included as the only fixed effect and study included as a random effect, restricted to the noise exposure range 40–65 dB L_{night}. Models were run separately for each traffic mode and disturbance question. The combined estimate was calculated using average responses of the awakening, falling asleep, and sleep disturbance questions within studies. Note: CI, confidence interval; L_{night}, nighttime noise; WHO, World Health Organization.

Table 6. GRADE Evidence profile (adapted from the WHO review[19]).

Domain	Criterion	Assessment	Grade change
Sleep disturbance questions: noise mentioned			
Start level	Longitudinal = high; others = low	All cross-sectional studies	Low quality
Study limitations	Majority of studies low quality	Aircraft and railway: majority of studies have low risk of selection bias (10/19) and exposure assessment bias (14/19)	Aircraft and railway: no downgrade
		Road: majority of studies have low risk of selection bias (11/15) and high risk of exposure assessment bias (10/15)	Road: downgrade one level
Inconsistency	Conflicting results; high I^2	High heterogeneity between studies ($I^2 \geq 85\%$)	Downgrade one level
Indirectness	Direct comparison; same PECO	Same PECO	No downgrade
Precision	CIs contain 25% harm or benefit	CIs narrower than 25% except for few outcomes at high noise levels	No downgrade
Publication bias	Indicated by funnel plot	Symmetrical plots	No downgrade
Judgment after downgrades	—	—	Aircraft, road, and railway: very low quality
Dose–response	Significant trend	Statistically significant trend for all outcomes	Upgrade one level
Magnitude of effect	RR > 2	OR > 2 for 11 of 12 outcomes	Upgrade one level
Confounding adjusted	Effect in spite of confounding working toward the null	Not observed	No upgrade
Overall judgment	—	—	Aircraft, road, and railway: moderate quality
Sleep disturbance questions: noise not mentioned			
Start level	Longitudinal = high; others = low	All cross-sectional studies	Low quality
Study limitations	Majority of studies low quality	Majority of studies have high risk of selection bias (10/18) and low risk of exposure assessment bias (15/18)	Downgrade one level
Inconsistency	Conflicting results; high I^2	Railway: unimportant heterogeneity between studies ($I^2 = 0\%$)	Railway: no downgrade
		Aircraft and road: substantial to considerable heterogeneity between studies ($65\% \leq I^2 \leq 75\%$)	Aircraft and road: downgrade one level
Indirectness	Direct comparison; same PECO	Same PECO	No downgrade
Precision	CIs contain 25% harm or benefit	Wide CIs	Downgrade one level
Publication bias	Indicated by funnel plot	Symmetrical plots	No downgrade
Judgment after downgrades	—	—	Aircraft, road, and railway: very low quality
Dose–response	Significant trend	Aircraft: statistically significant trend for falling asleep and combined estimate	Railway: no upgrade
		Railway: not significant	Aircraft and road: upgrade one level
		Road: statistically significant trend for awakenings, falling asleep and combined estimate	
Magnitude of effect	RR > 2	OR < 2 for all outcomes	No upgrade
Confounding adjusted	Effect in spite of confounding working toward the null	Not observed	No upgrade
Overall judgment	—	—	Railway: very low quality Aircraft and road: low quality

Note: —, not applicable; CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations (criteria); OR, odds ratio; PECO, Patient/Problem, Exposure, Comparison and Outcome (framework); RR, risk ratio; WHO, World Health Organization.

European, as were the majority of respondents across the studies of aircraft noise.[35,41,42,46] Although there was one study of aircraft noise from Asia,[32] and three from the United States,[20,21,45] these studies were small, with sample sizes ranging from $n = 33$ to $n = 559$. European studies continue to be overrepresented (Figure S3). However, we found no statistically significant differences in sleep disturbance between European and non-European studies. On one hand, this suggests that there are, in fact, no differences in response between the two locations, that the degree of sleep disturbance by noise is rather global in nature, and that results of the present analyses are relevant outside of Europe. Conversely, the point estimates were rather different between study location for several sleep disturbance outcomes. This could indicate underlying cultural differences in attitudes to noise and perceived sleep disturbance that have not been captured in studies to date. Future investigations outside of Europe may uncover relevant international differences, as well as increasing confidence that existing studies are representative of noise-induced sleep disturbance among these underinvestigated regions.

Considerations on Self-Reported Sleep Disturbance

Our overall findings of self-reported disturbance by noise should be treated with some caution when considering noise-induced effects on sleep. Sleep is, by its nature, an unconscious process, meaning that its subjective evaluation is difficult. Accordingly, there can be substantial differences between self-reported and physiologically derived measures of sleep and noise-induced sleep disturbance.[77–79] Self-report may also suffer from recall bias, particularly when questions relate to the preceding 12 months, as was typical for questions on sleep disturbance in most studies included in our meta-analysis. It is likely that responses to

Table 7. Summary of meta-analytic and evidence quality findings.

Sleep outcome	Noise source	Studies (n)[a]	Respondents (n)[a]	Quality of evidence	Noise metric	OR per 10-dB increase (95% CI)
Self-reported sleep disturbance in adults Noise specified as source of disturbance	Aircraft	11	19,488	Moderate	L_{night}	2.18 (2.01, 2.36)
	Road	14	31,738	Moderate	L_{night}	2.52 (2.28, 2.79)
	Railway	8	10,846	Moderate	L_{night}	2.97 (2.57, 3.43)
Self-reported sleep disturbance in adults Noise not specified as source of disturbance	Aircraft	8	2,571	Low	L_{night}	1.52 (1.20, 1.93)
	Road	7	38,380	Low	L_{night}	1.14 (1.08, 1.21)
	Railway	4	4,326	Very low	L_{night}	1.17 (0.91, 1.49)

Note: ORs were calculated in logistic regression models with L_{night} included as the only fixed effect and study included as a random effect, restricted to the noise exposure range 40–65 dB L_{night}. Models were run separately for each traffic mode and for sleep questionnaire outcomes that did or did not mention noise. Data shown are for the combined estimates calculated using average responses of the awakening, falling asleep, and sleep disturbance questions within studies. L_{night}, nighttime noise; OR, odds ratio.
[a]In the L_{night} range 40–65 dB for which ORs were calculated.

questions on these timescales are driven by noise exposure in the more recent past. However, self-reported sleep outcomes are methodologically convenient and inexpensive to implement in field studies, meaning that we could perform the meta-analysis with a number of studies and sample size that would not have been possible if focusing on physiologic outcomes. As such, we have higher confidence in the accuracy and representativeness of the analysis. A further advantage is that self-reported disturbance is a valuable end point per se, considered by the WHO as a primary health outcome. By focusing our analysis on these outcomes, the results may be useful in future estimates of the disease burden of environmental noise[80] and recommendations for nighttime noise limits,[15] both of which derive from self-reported sleep disturbance. Finally, self-reported outcomes capture habitual sleep quality and disturbance, unlike physiologic measurements that capture only acute effects within single nights. It does, however, remain unclear how long-term self-reported sleep disturbance by noise relates to overall health.

Future large-scale field studies with objective measurements of noise and sleep can offer mechanistic insights linking nocturnal noise, sleep disruption, and epidemiological observations of the development of cardiovascular and metabolic disease associated with exposure to environmental noise in addition to the derivation of exposure–response relationship s.[81] A better understanding of the underlying pathophysiological pathways is especially valuable when considering vulnerable populations who may be at increased risk of disturbance. These vulnerable groups include the elderly, who can suffer from age-related declines in sleep quantity and quality[82]; populations who may have already poor sleep quality, such as people with mental health or sleep disorders[83]; and populations with obesity, who are at increased risk of suffering from obstructive sleep apnea, as well as having increased risk for cardiometabolic diseases generally.[84,85] Infants, children, and adolescents can also be considered as vulnerable groups because of the importance of sleep of sufficient quality and duration for development.[80,86,87]

Limitations

Data could not be obtained for two studies that were initially deemed to be eligible for inclusion. It is unlikely that including the study of road traffic noise[44] would have substantially altered the updated relationships because the sample size was low ($n=225$) compared with the overall sample size for all road traffic studies ($n=31,738$). Including the study of aircraft noise,[43] however, may have altered the sleep outcomes where noise was not mentioned for falling asleep, sleep disturbance, and the combined estimate. Compared with sample sizes of $n=4,379$ for questions on falling asleep and just $n=195$ for sleep disturbance questions that were included in our analysis, the omitted study had a sample size of $n=2,831$, which would have reflected a substantial proportion of the total data set. The change in effect size that would have resulted from including this study is unclear because the relevant sleep-disturbance questions were single items that formed only part of the insomnia severity index (ISI). Because only overall results from the ISI were published, we do not know whether the relevant items were related to noise exposure, or to what extent.

A limitation of the meta-analysis was that many studies modeled noise exposure at the most exposed façade of the residence, and thus noise levels specifically at the bedroom façade are unknown. This means there is probably some exposure misclassification, with lower noise levels if the bedroom faces away from the noise source. This is more likely for road and railway noise than aircraft noise, with the latter source being less fixed in position relative to the bedroom. This would, in effect, shift the exposure–response curves to the left, leading to an increased probability of disturbance at lower noise levels, given that noise levels at the bedrooms are, on average, probably lower than assuming they are all positioned at the most exposed façade. This was supported by two studies in the meta-analysis that found that a lower proportion of respondents were highly sleep disturbed by road traffic noise[46] or reported insomnia symptoms[37] when the bedroom faced away from the street. Furthermore, disturbance was lower when the difference in noise level between the bedroom and the most exposed façade was greater.[46] A second limitation of the meta-analysis is that we did not adjust for potentially relevant effect modifiers. We adopted this approach so that results would be directly comparable to those in the WHO review, which also did not include such adjustments.[19] Sleep, and its disturbance by noise, may differ depending on age, sex, socioeconomic status, and preexisting sleep disorders. Further, sleep disturbance is not unique to noise exposure and may arise from other environmental stressors, including air pollution,[88–90] vibration (from, for instance, freight trains on railway lines),[91] light,[92] and temperature and humidity.[93,94] Future studies should consider the consequences of exposure to multiple stressors, and their interactions on sleep.

Summary of Evidence

Our main objective was to update the WHO meta-analysis on sleep disturbance by traffic noise with evidence published after 2015.[19] The main findings and quality of evidence are summarized in Table 7. There was a significant probability of being highly sleep disturbed by nocturnal noise from aircraft, road, and railway noise when the disturbance question mentioned noise, and the quality of evidence for these outcomes was moderate. Exposure–response curves were similar to the WHO review for road and railway noise in our updated analysis, and we found an increased probability of being highly sleep disturbed by aircraft noise at high noise levels. Because of the number of studies published since 2015, for the first time, we were able to generate exposure–response relationships for sleep outcomes that did not

explicitly mention noise. Point estimates for these outcomes were smaller than questions mentioning noise, and were often not statistically significant, and the quality of evidence was graded lower, from low to very low. Our findings do not suggest that the recent WHO recommendations for nighttime noise need to be revisited,[15] although quantitative assessments of sleep disturbance by aircraft noise at high exposure levels should consider the implications of our analysis. We did not find significant indications of international differences in sleep disturbance by noise, but future large-scale studies in non-European nations may necessitate a reevaluation of the evidence.

Acknowledgments

Contributions of the authors are as follows—M.G.S.: investigation, formal analysis, data curation, writing (original draft), and visualization; M.C.: investigation and writing (review and editing); and M.B.: conceptualization, methodology, formal analysis, writing (review and editing), supervision, and funding acquisition.

We are grateful to G.M. Aasvang, J. Evandt, T.L. Nguyen, M. Reedijk, D. Schreckenberg, R. Vermeulen, K. Persson Waye, S. Bartels, and S. Fredriksson for sharing additional deidentified self-reported sleep data from their studies to facilitate the updated meta-analysis. We also thank T. Bodin, M. Brink, L. Brown, J. Halonen, J. Hong, T.L. Nguyen, G. Ristovska, M. Röösli, D. Schreckenberg, and T. Yano, who graciously shared sleep data for the original WHO meta-analysis, which was included in this updated analysis.

This work was funded by the Department for Environmental, Food and Rural Affairs (DEFRA) on behalf of the Interdepartmental Group on Costs and Benefits Noise Subject Group, project no. 30116. DEFRA had no role in designing the study or collection, analysis, and interpretation of data. DEFRA had the opportunity to comment on a draft of this manuscript, but made no substantive edits. M.C. was supported by the National Institutes of Health/National Institute of Nursing Research (K99NR019862).

The information and views set out in this report are those of the authors and do not necessarily reflect the official opinion of DEFRA. DEFRA does not guarantee the accuracy of the data included in this review. Neither DEFRA nor any person acting on behalf of DEFRA may be held responsible for the use which might be made of the information contained therein.

References

1. Consensus Conference Panel; Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, et al. 2015. Joint Consensus Statement of the American Academy of Sleep Medicine and Sleep Research Society on the recommended amount of sleep for a healthy adult: methodology and discussion. Sleep 38(8):1161–1183, PMID: 26194576, https://doi.org/10.5665/sleep.4886.
2. Banks S, Dinges DF. 2007. Behavioral and physiological consequences of sleep restriction. J Clin Sleep Med 3(5):519–528, PMID: 17803017, https://doi.org/10.5664/jcsm.26918.
3. Dettoni JL, Consolim-Colombo FM, Drager LF, Rubira MC, Cavasin de Souza SBP, Irigoyen MC, et al. 2012. Cardiovascular effects of partial sleep deprivation in healthy volunteers. J Appl Physiol (1985) 113(2):232–236, PMID: 22539169, https://doi.org/10.1152/japplphysiol.01604.2011.
4. Buxton OM, Cain SW, O'Connor SP, Porter JH, Duffy JF, Wang W, et al. 2012. Adverse metabolic consequences in humans of prolonged sleep restriction combined with circadian disruption. Sci Transl Med 4(129):129ra43, PMID: 22496545, https://doi.org/10.1126/scitranslmed.3003200.
5. 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(9):2126–2133, PMID: 20585000, https://doi.org/10.2337/db09-0699.
6. Taheri S, Lin L, Austin D, Young T, Mignot E. 2004. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Med 1(3):e62, PMID: 15602591, https://doi.org/10.1371/journal.pmed.0010062.
7. Diekelmann S, Born J. 2010. The memory function of sleep. Nat Rev Neurosci 11(2):114–126, PMID: 20046194, https://doi.org/10.1038/nrn2762.
8. Cappuccio FP, Taggart FM, Kandala NB, Currie A, Peile E, Stranges S, et al. 2008. Meta-analysis of short sleep duration and obesity in children and adults. Sleep 31(5):619–626, PMID: 18517032, https://doi.org/10.1093/sleep/31.5.619.
9. Knutson KL, Spiegel K, Penev P, Van Cauter E. 2007. The metabolic consequences of sleep deprivation. Sleep Med Rev 11(3):163–178, PMID: 17442599, https://doi.org/10.1016/j.smrv.2007.01.002.
10. Gottlieb DJ, Redline S, Nieto FJ, Baldwin CM, Newman AB, Resnick HE, et al. 2006. Association of usual sleep duration with hypertension: the Sleep Heart Health Study. Sleep 29(8):1009–1014, PMID: 16944668, https://doi.org/10.1093/sleep/29.8.1009.
11. Badran M, Yassin BA, Fox N, Laher I, Ayas N. 2015. Epidemiology of sleep disturbances and cardiovascular consequences. Can J Cardiol 31(7):873–879, PMID: 26037823, https://doi.org/10.1016/j.cjca.2015.03.011.
12. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. 2010. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. Sleep 33(5):585–592, PMID: 20469800, https://doi.org/10.1093/sleep/33.5.585.
13. Ferrie JE, Shipley MJ, Akbaraly TN, Marmot MG, Kivimäki M, Singh-Manoux A. 2011. Change in sleep duration and cognitive function: findings from the Whitehall II Study. Sleep 34(5):565–573, PMID: 21532949, https://doi.org/10.1093/sleep/34.5.565.
14. WHO (World Health Organization) Regional Office for Europe. 2011. *Burden of Disease from Environmental Noise. Quantification of Healthy Life Years Lost in Europe.* Copenhagen, Denmark: World Health Organization Regional Office for Europe.
15. WHO Regional Office for Europe. 2018. *Environmental Noise Guidelines for the European Region.* Copenhagen, Denmark: World Health Organization Regional Office for Europe.
16. Hänninen O, Knol AB, Jantunen M, Lim TA, Conrad A, Rappolder M, et al. 2014. Environmental burden of disease in Europe: assessing nine risk factors in six countries. Environ Health Perspect 122(5):439–446, PMID: 24584099, https://doi.org/10.1289/ehp.1206154.
17. U.S. Department of Transportation Bureau of Transport Statistics. 2020. Under a quarter of population exposed to office-type transportation noise. https://www.bts.gov/newsroom/under-quarter-population-exposed-office-type-transportation-noise [accessed 19 March 2021].
18. 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(1):54–63, PMID: 29037963, https://doi.org/10.1016/j.ijheh.2017.10.003.
18. 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(3):519, PMID: 29538344, https://doi.org/10.3390/ijerph15030519.
20. Basner M, Witte M, McGuire S. 2019. Aircraft noise effects on sleep—results of a pilot study near Philadelphia International Airport. Int J Environ Res Public Health 16(17):3178, PMID: 31480420, https://doi.org/10.3390/ijerph16173178.
21. Smith MG, Rocha S, Witte M, Basner M. 2020. On the feasibility of measuring physiologic and self-reported sleep disturbance by aircraft noise on a national scale: a pilot study around Atlanta airport. Sci Total Environ 718:137368, PMID: 32092522, https://doi.org/10.1016/j.scitotenv.2020.137368.
22. 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(5 pt 1):2772–2784, PMID: 16708935, https://doi.org/10.1121/1.2184247.
23. Münzel T, Gori T, Babisch W, Basner M. 2014. Cardiovascular effects of environmental noise exposure. Eur Heart J 35(13):829–836, PMID: 24616334, https://doi.org/10.1093/eurheartj/ehu030.
24. Kröller-Schön S, Daiber A, Steven S, Oelze M, Frenis K, Kalinovic S, 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(38):3528–3539, PMID: 29905797, https://doi.org/10.1093/eurheartj/ehy333.
25. Münzel T, Kröller-Schön S, Oelze M, Gori T, Schmidt FP, Steven S, et al. 2020. Adverse cardiovascular effects of traffic noise with a focus on nighttime noise and the new WHO noise guidelines. Annu Rev Public Health 41(1):309–328, PMID: 31922930, https://doi.org/10.1146/annurev-publhealth-081519-062400.
26. Basner M, Babisch W, Davis A, Brink M, Clark C, Janssen S, et al. 2014. Auditory and non-auditory effects of noise on health. Lancet 383(9925):1325–1332, PMID: 24183105, https://doi.org/10.1016/S0140-6736(13)61613-X.
27. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372:n71, PMID: 33782057, https://doi.org/10.1136/bmj.n71.
28. van Kamp I, Simon S, Notley H, Baliatsas C, van Kempen E. 2020. Evidence relating to environmental noise exposure and annoyance, sleep disturbance, cardio-vascular and metabolic health outcomes in the context of IGCB (N): a scoping review of new evidence. Int J Environ Res Public Health 17(9):3016, PMID: 32357581, https://doi.org/10.3390/ijerph17093016.

29. European Council. 2002. Directive 2002/49/EC of the European Parliament and of the Council of 25 June 2002 relating to the assessment and management of environmental noise. Off J Eur Communities L 189:12–24. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32002L0049 [accessed 22 June 2022].
30. Fields JM, De Jong RG, Gjestland T, Flindell IH, Job RFS, Kurra S, et al. 2001. Standardized general-purpose noise reaction questions for community noise surveys: research and a recommendation. J Sound Vib 242(4):641–679, https://doi.org/10.1006/jsvi.2000.3384.
31. Roth T. 2007. Insomnia: definition, prevalence, etiology, and consequences. J Clin Sleep Med 3(suppl 5):S7–S10, PMID: 17824495, https://doi.org/10.5664/jcsm.26 929.
32. Nguyen TL, Trieu BL, Hiraguri Y, Morinaga M, Morihara T, Yano T. 2020. Effects of changes in acoustic and non-acoustic factors on public health and reactions: follow-up surveys in the vicinity of the Hanoi Noi Bai International Airport. Int J Environ Res Public Health 17(7):2597, PMID: 32290317, https://doi.org/10.3390/ijerph17072597.
33. Bodin T, Björk J, Ardö J, Albin M. 2015. Annoyance, sleep and concentration problems due to combined traffic noise and the benefit of quiet side. Int J Environ Res Public Health 12(2):1612–1628, PMID: 25642690, https://doi.org/10.3390/ijerph120201612.
34. Martens AL, Reedijk M, Smid T, Huss A, Timmermans D, Strak M, et al. 2018. Modeled and perceived RF-EMF, noise and air pollution and symptoms in a population cohort. Is perception key in predicting symptoms? Sci Total Environ 639:75–83, PMID: 29778684, https://doi.org/10.1016/j.scitotenv.2018.05.007.
35. Carugno M, Imbrogno P, Zucchi A, Ciampichini R, Tereanu C, Sampietro G, et al. 2018. Effects of aircraft noise on annoyance, sleep disorders, and blood pressure among adult residents near the Orio al Serio International Airport (BGY), Italy. Med Lav 109(4):253–263, PMID: 30168498, https://doi.org/10.23749/mdl.v109i4.7271.
36. Filomena V, De Vivo L, Notarnicola L, Aversano R, Tusciano M. 2014. Noise assessment in the neighbourhood of Italian military airports. In: *Proceedings of the 43rd International Congress on Noise Control Engineering: INTER.NOISE 2014.* Davy J, Don C, McMinn T, Dowsett L, Broner N, Burgess M, eds. 16–19 November 2014. Australian Capital Territory, Australia: Australian Acoustical Society, 260.
37. Evandt J, Oftedal B, Hjertager Krog N, Nafstad P, Schwarze PE, Aasvang GM. 2017. A population-based study on nighttime road traffic noise and insomnia. Sleep 40(2):zsw055, PMID 28364487, https://doi.org/10.1093/sleep/zsw055.
38. National Heart, Lung, and Blood Institute. 2021. Study quality assessment tools: quality assessment tool for observational cohort and cross-sectional studies. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools [accessed 4 May 2021].
39. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. (eds.). 2021. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 6.2 (updated February 2021). London, UK: Cochrane Collaboration.
40. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. 2008. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336(7650):924–926, PMID: 18436948, https://doi.org/10.1136/bmj.39489.470347.AD.
41. Civil Aviation Authority. 2017. *Survey of Noise Attitudes 2014: Aircraft Noise and Annoyance*. 2nd ed. CAP 1506. http://publicapps.caa.co.uk/modalapplication.aspx?appid=11&mode=detail&id=7744.
42. NORAH (Noise-Related Annoyance, Cognition, and Health). 2021. Overview of results from the NORAH sleep study. http://www.laermstudie.de/ergebnisse/ergebnisse-schlafstudie/ueberblick/ [accessed 22 June 2022].
43. Kwak KM, Ju YS, Kwon YJ, Chung YK, Kim BK, Kim H, et al. 2016. The effect of aircraft noise on sleep disturbance among the residents near a civilian airport: a cross-sectional study. Ann Occup Environ Med 28(1):38, PMID: 27595005, https://doi.org/10.1186/s40557-016-0123-2.
44. Paiva KM, Cardoso MRA, Zannin PHT. 2019. Exposure to road traffic noise: annoyance, perception and associated factors among Brazil's adult population. Sci Total Environ 650(pt 1):978–986, PMID: 30308872, https://doi.org/10.1016/j.scitotenv.2018.09.041.
45. Rocha S, Smith MG, Witte M, Basner M. 2019. Survey results of a pilot sleep study near Atlanta International Airport. Int J Environ Res Public Health 16(22):4321, PMID: 31698800, https://doi.org/10.3390/ijerph16224321.
46. Brink M, Schäffer B, Vienneau D, Pieren R, Foraster M, Eze IC, et al. 2019. Self-reported sleep disturbance from road, rail and aircraft noise: exposure-response relationships and effect modifiers in the SiRENE study. Int J Environ Res Public Health 16(21):4186, PMID: 31671890, https://doi.org/10.3390/ijerph16214186.
47. Bartels S, Ögren M, Kim JL, Fredriksson S, Persson Waye K. 2021. The impact of nocturnal road traffic noise, bedroom window orientation, and work-related stress on subjective sleep quality: results of a cross-sectional study among women. Int Arch Occup Environ Health 94(7):1523–1536, PMID: 34043056, https://doi.org/10.1007/s00420-021-01696-w.
48. Nguyen LT, Nguyen TL, Yano T, Morinaga M, Yamada I, Tetsumi S, et al. 2015. Social surveys around Noi Bai Airport before and after the opening of a new terminal building. In: *Proceedings of the 44th International Congress on Noise Control Engineering (Internoise 2015)*. Burroughs C, ed. 9–12 August 2015. Reston, VA: Institute of Noise Control Engineering, 4270.
49. Yano T, Nguyen TL, Nguyen TL, Takada M, Yamada I, Morinaga M, et al. 2015. Community response to a step change in aircraft noise exposure: The first socio-acoustic survey around Noi Bai Airport in Hanoi. In: *Proceedings of the International Congress on Sound and Vibration (22ICSV)*, Florence, Italy,12–16 July 2015.
50. Nguyen TL, Yano T, Nguyen HQ, Nguyen KTT, Fukushima H, Kawai K, et al. 2012. Aircraft and road traffic noise annoyance in Da Nang City, Vietnam. In: *Proceedings of the 41st International Congress and Exposition on Noise Control Engineering 2012 (INTER-NOISE 2012)*. Burroughs C, Conlon S, eds. 19–22 August 2012. Indianapolis, IN: Institute of Noise Control Engineering, 1661.
51. Nguyen TL, Yano T, Nguyen HQ, Hoang TL, Nishimura T, Morihara T, et al. 2010. Community response to aircraft and combined noises in Hanoi. In: *Proceedings of the 39th International Congress on Noise Control Engineering 2010 (INTER-NOISE 2010)*. 13–16 June 2010. Lisbon, Portugal: Sociedade Portuguesa de Acustica, 4038.
52. Nguyen TL, Yano T, Nguyen HQ, Nishimura T, Fukushima H, Sato T, et al. 2011. Community response to aircraft noise in Ho Chi Minh City and Hanoi. Appl Acoust 72(11):814–822, https://doi.org/1 0101 6/j.apacoust.2011.05.002.
53. Yano T, Nguyen TL, Nishimura T, Sato T. 2019. Social survey on community response to aircraft noise in Ho Chi Minh City. In: *Proceedings of the 38th International Congress and Exposition on Noise Control Engineering 2009 (INTER-NOISE 2009)*. Bolton JS, Burroughs C, Gover B, eds. 23–26 August 2009. Ashland, OH: Noise Control Foundation, 482.
54. Schreckenberg D, Heudorf U, Eikmann T, Herr C, Nieden A, Meis M. 2009. Aircraft noise and health of residents living in the vicinity of Frankfurt airport. In: *Proceedings of the 8th European Conference on Noise Control 2009 (EURONOISE 2009)*. 26–28 October 2009. St. Albans Hertfordshire, UK: Institute of Acoustics, 511.
55. Brink M, Wirth K, Rometsch R, Schierz C. 2005. *Lärmstudie 2000: Zusammenfassung* [In German]. Zurich, Switzerland: Institute for Organizational and Occupational Sciences (ZOA).
56. Brink M. 2011. Parameters of well-being and subjective health and their relationship with residential traffic noise exposure—a representative evaluation in Switzerland. Environ Int 37(4):723–733, PMID: 21419495, https://doi.org/10.1016/j.envint.2011.02 011.
57. Phan HYT, Yano T, Phan HAT, Nishimura T, Sato T, Hashimoto Y. 2010. Community responses to road traffic noise in Hanoi and Ho Chi Minh City. Appl Acoust 71(2):107–114, https://doi.org/10.1016/j.apacoust.2009.08.004.
58. Shimoyama K, Nguyen TL, Yano T, Morihara T. 2014. Social surveys on community response to road traffic in five cities in Vietnam. In: *Proceedings of the 43rd International Congress on Noise Control Engineering: INTER.NOISE 2014*. Davy J, Don C, McMinn T, Dowsett L, Broner N, Burgess M, eds. 16–19 November 2014. Australian Capital Territory, Australia: Australian Acoustical Society, 109.
59. Sato T, Yano T, Björkman M, Rylander R. 2002. Comparison of community response to road traffic noise in Japan and Sweden—part I: outline of surveys and dose–response relationships. J Sound Vib 250(1):161–167, https://doi.org/10.1006/jsvi.2001.3892.
60. Brown AL, Lam KC, van Kamp I. 2015. Quantification of the exposure and effects of road traffic noise in a dense Asian city: a comparison with Western cities. Environ Health 14(1):22, PMID: 25889117, https://doi.org/10.1186/s12940-015-0009-8.
61. Hong J, Kim J, Lim C, Kim K, Lee S. 2010. The effects of long-term exposure to railway and road traffic noise on subjective sleep disturbance. J Acoust Soc Am 128(5):2829–2835, PMID: 21110578, https://doi.org/10.1121/1.3493437.
62. Ristovska G, Gjorgjev D, Stikova E, Petrova V, Cakar MD. 2009. Noise induced sleep disturbance in adult population: cross sectional study in Skopje urban centre. Maced J Med Sci 2(3):255–260. http://www.mjms.mk/Online/MJMS_2009_2_3/MJMS.1857-5773.2009-0060.pdf [accessed 22 June 2022].
63. Freiр, 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(2–3):188–195, PMID: 23684342, https://doi.org/10.1016/j.ijheh.2013.04.003.
64. Halonen JI, Vahtera J, Stansfeld S, Yli-Tuomi T, Salo P, Pentti J, et al. 2012. Associations between nighttime traffic noise and sleep: the Finnish public sector study. Environ Health Perspect 120(10):1391–1396, PMID: 22871637, https://doi.org/10.1289/ehp.1205026.
65. Sato T, Yano T, Morihara T, Masden K. 2004. Relationships between rating scales, question stem wording, and community responses to railway noise. J Sound Vib 277(3):609–616, https://doi.org/10.1016/j.jsv.2004.03.023 .
66. Schreckenberg D. 2013. Exposure–response rela tons hip for railway noise annoyance in the Middle Rhine Valley. In: *Proceedings of the 42nd International Congress and Exposition on Noise Control Engineering 2013 (INTER-NOISE 2013)*. 15–18 September 2013. Vienna, Austria: Austrian Noise Abatement Association, 4716.

67. Smith MG, Younes M, Aeschbach D, Elmenhorst EM, Müller U, Basner M. 2022. Traffic noise-induced changes in wake-propensity measured with the Odds-Ratio Product (ORP). Sci Total Environ 805:150191, PMID: 34818802, https://doi.org/10.1016/j.scitotenv.2021.150191.
68. Marks A, Griefahn B. 2007. Associations between noise sensitivity and sleep, subjectively evaluated sleep quality, annoyance, and performance after exposure to nocturnal traffic noise. Noise Health 9(34):1–7, PMID: 17851221, https://doi.org/10.4103/1463-1741.34698.
69. Li S, Fong DYT, Wong JYH, McPherson B, Lau EYY, Huang L, et al. 2021. Noise sensitivity associated with nonrestorative sleep in Chinese adults: a cross-sectional study. BMC Public Health 21(1):643, PMID: 33794830, https://doi.org/10.1186/s12889-021-10667-2.
70. Park J, Chung S, Lee J, Sung JH, Cho SW, Sim CS. 2017. Noise sensitivity, rather than noise level, predicts the non-auditory effects of noise in community samples: a population-based survey. BMC Public Health 17(1):315, PMID: 28403870, https://doi.org/10.1186/s12889-017-4244-5.
71. Czajka JL, Beyler A. 2016. *Background Paper: Declining Response Rates in Federal Surveys: Trends and Implications*. Reference No. 40146.D4C. 15 June 2016. Washington, DC: Mathematica Policy Research. https://aspe.hhs.gov/sites/default/files/private/pdf/255531/Decliningresponserates.pdf [accessed 22 June 2022].
72. Dillman DA, Smyth JD, Christian LM. 2014. *Internet, Phone, Mail, and Mixed-Mode Surveys: The Tailored Design Method*. 4th ed. Indianapolis, IN: John Wiley & Sons.
73. Groves RM, Peytcheva E. 2008. The impact of nonresponse rates on nonresponse bias: a meta-analysis. Public Opin Q 72(2):167–189, https://doi.org/10.1093/poq/nfn011.
74. Cook C, Heath F, Thompson RL. 2000. A meta-analysis of response rates in web- or internet-based surveys. Educ Psychol Meas 60(6):821–836, https://doi.org/10.1177/00131640021970934.
75. 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(12):1539, PMID: 29292769, https://doi.org/10.3390/ijerph14121539.
76. Peris E, Fenech B. 2020. Associations and effect modification between transportation noise, self-reported response to noise and the wider determinants of health: a narrative synthesis of the literature. Sci Total Environ 748:141040, PMID: 33113703, https://doi.org/10.1016/j.scitotenv.2020.141040.
77. Silva GE, Goodwin JL, Sherrill DL, Arnold JL, Bootzin RR, Smith T, et al. 2007. Relationship between reported and measured sleep times: the Sleep Heart Health Study (SHHS). J Clin Sleep Med 3(6):622–630, PMID: 17993045, https://doi.org/10.5664/jcsm.26974.
78. Basner M, Müller U, Elmenhorst EM. 2011. Single and combined effects of air, road, and rail traffic noise on sleep and recuperation. Sleep 34(1):11–23, PMID: 21203365, https://doi.org/10.1093/sleep/34.1.11.
79. Smith MG, Ögren M, Thorsson P, Hussain-Alkhateeb L, Pedersen E, Forssén J, et al. 2020. A laboratory study on the effects of wind turbine noise on sleep: results of the polysomnographic WiTNES study. Sleep 43(9):zsaa046, PMID: 32211778, https://doi.org/10.1093/sleep/zsaa046.
80. Fritschi L, Brown AL, Kim R, Schwela DH, Kephalopoulos S. 2011. *Burden of Disease from Environmental Noise: Quantification of Healthy Life Years Lost in Eupope*. Copenhagen, Denmark: World Health Organization.
81. van Kempen E, 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(2):379, PMID: 29470452, https://doi.org/10.3390/ijerph15020379.
82. Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. 2004. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep 27(7):1255–1273. 73, PMID: 15586779, https://doi.org/10.1093/sleep/27.7.1255.
83. Sygna K, Aasvang GM, Aamodt G, Oftedal B, Krog NH. 2014. Road traffic noise, sleep and mental health. Environ Res 131:17–24, PMID: 24637180, https://doi.org/10.1016/j.envres.2014.02.010.
84. Drager LF, Togeiro SM, Polotsky VY, Lorenzi-Filho G. 2013. Obstructive sleep apnea: a cardiometabolic risk in obesity; and the metabolic syndrome. J Am Coll Cardiol 62(7):569–576, PMID: 23770180, https://doi.org/10.1016/j.jacc.2013.05.045.
85. Klein S, Allison DB, Heymsfield SB, Kelley DE, Leibel RL, Nonas C, et al. 2007. Waist circumference and cardiometabolic risk: a consensus statement from Shaping America's Health: Association for Weight Management and Obesity Prevention; NAASO, the Obesity Society; the American Society for Nutrition; and the American Diabetes Association. Am J Clin Nutr 85(5):1197–1202, PMID: 17490953, https://doi.org/10.1093/ajcn/85.5.1197.
86. Scher A. 2005. Infant sleep at 10 months of age as a window to cognitive development. Early Hum Dev 81(3):289–292, PMID: 15814211, https://doi.org/10.1016/j.earlhumdev.2004.07.005.
87. Tarokh L, Saletin JM, Carskadon MA. 2016. Sleep in adolescence: physiology, cognition and mental health. Neurosci Biobehav Rev 70:182–188, PMID: 27531236, https://doi.org/10.1016/j.neubiorev.2016.08.008.
88. Wei F, Nie G, Zhou B, Wang L, Ma Y, Peng S, et al. 2017. Association between Chinese cooking oil fumes and sleep quality among a middle-aged Chinese population. Environ Pollut 227:543–551, PMID: 28501768, https://doi.org/10.1016/j.envpol.2017.05.018.
89. Shen YL, Liu WT, Lee KY, Chuang HC, Chen HW, Chuang KJ. 2018. Association of $PM_{2.5}$ with sleep-disordered breathing from a population-based study in Northern Taiwan urban areas. Environ Pollut 233:109–113, PMID: 29059625, https://doi.org/10.1016/j.envpol.2017.10.052.
90. Strøm-Tejsen P, Zukowska D, Wargocki P, Wyon DP. 2016. The effects of bedroom air quality on sleep and next-day performance. Indoor Air 26(5):679–686, PMID: 26452168, https://doi.org/10.1111/ina.12254.
91. Persson Waye K, Smith MG, Hussain-Alkhateeb L, Koopman A, Ögren M, Peris E, et al. 2019. Assessing the exposure-response relationship of sleep disturbance and vibration in field and laboratory settings. Environ Pollut 245:558–567, PMID: 30469126, https://doi.org/10.1016/j.envpol.2018.09.082.
92. Cho JR, Joo EY, Koo DL, Hong SB. 2013. Let there be no light: the effect of bedside light on sleep quality and background electroencephalographic rhythms. Sleep Med 14(12):1422–1425, PMID: 24210607, https://doi.org/10.1016/j.sleep.2013.09.007.
93. Haskell EH, Palca JW, Walker JM, Berger RJ, Heller HC. 1981. The effects of high and low ambient temperatures on human sleep stages. Electroencephalogr Clin Neurophysiol 51(5):494–501, PMID: 6165549, https://doi.org/10.1016/0013-4694(81)90226-1.
94. Okamoto-Mizuno K, Mizuno K, Michie S, Maeda A, Iizuka S. 1999. Effects of humid heat exposure on human sleep stages and body temperature. Sleep 22(6):767–773, PMID: 10505822, https://doi.org/10.1093/sleep/22.6.767.

SLEEP, 2024, 47, 1–3
https://doi.org/10.1093/sleep/zsad314
Advance access publication 11 December 2023
Editorial

Editorial

The effects on sleep play a critical role in the long-term health consequences of noise exposure

Mathias Basner[1,*] and Michael G. Smith[2]

[1]Unit for Experimental Psychiatry, Division of Sleep and Chronobiology, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA and
[2]School of Public Health and Community Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[*]Corresponding author: Mathias Basner, Unit for Experimental Psychiatry, Division of Sleep and Chronobiology, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA. Email: basner@pennmedicine.upenn.edu.

Sleep is a very dangerous state from an evolutionary perspective as we are unconscious and it takes time to arouse from sleep and react to threats in a meaningful way. Thus, it is not surprising that our full sensory array continues to monitor our environment during sleep, always ready to wake us up (although with different sensitivity depending on sleep stage). In fact, the multiple brief awakenings a healthy sleeper experiences during the night [1] can be thought of as "brief checks" into our sleep environment. As a long-range sensor, the auditory system plays a critical role in monitoring the environment during sleep. It analyzes not only sound levels but also sound content during sleep [2]. The thalamus has a gating function, shielding the cortex from sensory content deemed irrelevant, often associated with a K-complex in the electroencephalogram [3]. We do habituate to noise, but still react to individual noise events during sleep even after long exposure periods (i.e. years), albeit with lower probabilities. Compared to cortical arousals, autonomic arousals habituate to a much lesser degree with likely implications for long-term health consequences (see below) [4].

While the watchman function of the auditory system has served us well on our evolutionary journey, it is less relevant in modern societies where humans sleep in solid housing structures, safe from predators. However, there is no way to switch off biology that has evolved over millennia. Countless studies have unequivocally shown that exposure to traffic noise disturbs sleep and impairs sleep recuperation, without posing any obvious threat [5, 6]. Sensitivity to noise-induced sleep disturbance varies substantially inter-individually [7]. Interestingly, there seems to be a "sweet spot" for the propensity to arouse to internal or external stimuli, with mortality increasing for both very low (e.g. more severe oxygen desaturations in OSA patients?) and very high (e.g. higher degree of noise-induced sleep disturbance?) propensities [8].

At the same time, numerous epidemiological studies have demonstrated associations between environmental noise exposure and long-term health consequences, including cardiovascular disease [9], diabetes [10], cancer [11], and neurodegenerative disease [12]. It is likely no coincidence that short or low-quality sleep has been associated with the same disease endpoints. Recent animal research suggests that intermittent noise exposure during the night is the culprit for the pathophysiological changes that predispose to negative health consequences, while continuous noise exposure or exposure during the day elicited no or much smaller effects [13]. The observed changes include oxidative stress-induced vascular and brain damage, uncoupling of endothelial and neuronal nitric oxide synthase, vascular/brain infiltration with inflammatory cells, and changes in circadian rhythms [14], which all provide biologic plausibility for the associations observed in epidemiological studies. Endothelial dysfunction was also found in human participants after a single night of noise exposure [15], with stronger effects in patients with preexisting cardiovascular conditions [16], and partially mediated by Vitamin C application indicating the involvement of reactive oxygen species in causing vascular dysfunction. Aircraft noise can also trigger acute cardiac events during sleep which constitutes another mechanism of how noise exposure can contribute to cardiovascular mortality [17].

In a Perspectives piece published in this issue of *SLEEP* [18], Ellenbogen et al. discuss the effects of wind turbine noise on sleep, and they do a remarkable job in making their text accessible to laypeople including engineers with limited knowledge of sleep and sleep researchers with limited knowledge on sound measurement and prediction. Noise is defined as unwanted and/or harmful sound [19], stressing that both sound perception and the degree of control over the noise source can affect the reaction to noise. It is thus no surprise that an emotional response to noise mediated by the Amygdala likely plays a key role in major adverse cardiovascular events [20]. The societal discourse about noise is equally emotional, stressing the importance of noise-effects research as a "fact-deliverer" that can inform political and legislative decision-making. The latter is not an easy task and a balancing act, as a noise source typically also generates benefits for a group of individuals or society at large. For example, while aircraft generate noise, airports and airlines also create jobs and revenue, and for many it is very convenient to live close to an

airport. Likewise, clean energy produced by wind turbines is critical in the fight against climate change.

Ellenbogen et al. [18] perform a narrative review of recent studies on the effects of wind turbine noise on sleep and suggest that "noise from wind turbines measured outside the residence, up to 46 dBA (or modeled up to 49 dBA using the new standard), poses no risk to human sleep." One wonders how this suggestion compares to existing "official" limit values? Limits exist in many countries and provinces worldwide, for example, 37-44 dBA in Denmark, 45 dBA in Victoria, Australia, and 40-51 dBA in Ontario, Canada. These limits are often contingent on wind speed, with limits allowing for higher noise levels at higher speeds, and also the area in which wind turbines are sited, with limits demanding lower noise levels in quiet rural areas and areas which are primarily residential compared with more industrial or urban locations. In the United States, however, limits for wind turbine noise do not exist, at least not at the federal level. The Noise Control Act of 1972 (42 U.S.C. § 4901) is supposed to protect Americans from noise that jeopardizes their health and welfare. However, the Office of Noise Abatement and Control at the Environmental Protection Agency was defunded by the Reagan administration in 1982 and continues to be without funding. Since then federal guidance in developing, funding, disseminating, and coordinating information about the serious health impacts of noise has been imperceptible despite a continued congressional mandate. This includes the mandate to "conduct or finance research [. . .] on the effects, measurement, and control of noise, including but not limited to [. . .] investigation of the psychological and physiological effects of noise on humans [. . .] and the determination of dose/response relationships suitable for use in decision making, with special emphasis on the nonauditory effects" (quoted from the Noise Control Act). These dose/response relationships have mostly been generated in Europe and Asia, although other U.S. federal agencies have started to step in (e.g. [21]). Noise policy should be reviewed on a regular basis, include a review of the current literature and various stakeholders (i.e. those affected by noise, those generating noise, health organizations, researchers, and federal agencies). This is even more important as noise is also a justice and equity issue, disproportionally burdening underserved and low-income groups.

The importance of the environment for sleep quality cannot be overstated. In addition to noise, other factors like temperature and air quality play important roles [22]. Studies that inform health impact assessments are critically needed, but we also need to better understand whether noise mitigation strategies work. Noise reduction at the source is the best way of addressing noise effects, but it is sometimes either technically infeasible or too expensive. We therefore need to understand whether simpler and less expensive noise mitigation measures (e.g. sound insulation, white noise [23], and earplugs) are effective in reducing the effects of noise on sleep. Ellenbogen et al. [18] are to be commended for communicating a complex issue to a lay audience, sleep researchers, and engineers alike, and offering a limited value for further discussion.

Disclosure Statement

Financial Disclosure: Dr. Basner recently consulted for Tom Phillips + Associates in relation to traffic curfews at Dublin Airport and their effects on sleep. Dr. Smith has no financial conflicts of interest to declare. Nonfinancial Disclosure: None.

References

1. Bonnet M, Arand DL. EEG arousal norms by age. *J Clin Sleep Med*. 2007;**3**:271–274.
2. Türker B, Musat EM, Chabani E, *et al*. Behavioral and brain responses to verbal stimuli reveal transient periods of cognitive integration of the external world during sleep. *Nat Neurosci*. 2023;**26**:1981–1993. doi:10.1038/s41593-023-01449-7
3. Lechat B, Hansen K, Micic G, *et al*. K-complexes are a sensitive marker of noise-related sensory processing during sleep: A pilot study. *Sleep*. 2021;**44**. doi: 10.1093/sleep/zsab065
4. Basner M, Müller U, Elmenhorst EM. Single and combined effects of air, road, and rail traffic noise on sleep and recuperation. *Sleep*. 2011;**34**:11–23. doi: 10.1093/sleep/34.1.11
5. Muzet A. Environmental noise, sleep and health. *Sleep Med Rev*. 2007;**11**:135–142. doi: 10.1016/j.smrv.2006.09.001
6. Basner, M. Effects of noise on sleep. In: Kushida CA, ed. *Encyclopedia of Sleep and Circadian Rhythms*. 2nd ed. (SLS2), vol. **1**. Cambridge, MA: Elsevier, Academic Press; 2023: 258–268.
7. McGuire S, Müller U, Elmenhorst EM, Basner M. Inter-individual differences in the effects of aircraft noise on sleep fragmentation. *Sleep*. 2016;**39**:1107–1110. doi: 10.5665/sleep.5764
8. Shahrbabaki SS, Linz D, Hartmann S, Redline S, Baumert M. Sleep arousal burden is associated with long-term all-cause and cardiovascular mortality in 8001 community-dwelling older men and women. *Eur Heart J*. 2021;**42**:2088–2099. doi: 10.1093/eurheartj/ehab151
9. Munzel T, Sorensen M, Daiber A. Transportation noise pollution and cardiovascular disease. *Nat Rev Cardiol*. 2021;**18**:619–636. doi: 10.1038/s41569-021-00532-5
10. Liu C, Li W, Chen X, *et al*. Dose-response association between transportation noise exposure and type 2 diabetes: A systematic review and meta-analysis of prospective cohort studies. *Diabetes Metab Res Rev*. 2023;**39**:e3595. doi: 10.1002/dmrr.3595
11. Abbasi M, Yazdanirad S, Dehdarirad H, Hughes D. Noise exposure and the risk of cancer: A comprehensive systematic review. *Rev Environ Health*. 2023;**38**.713–726. doi: 10.1515/reveh-2022-0021
12. Huang L, Zhang Y, Wang Y, Lan Y. Relationship between chronic noise exposure, cognitive impairment, and degenerative dementia: Update on the experimental and epidemiological evidence and prospects for further research. *J Alzheimers Dis*. 2021;**79**:1409–1427. doi: 10.3233/JAD-201037
13. Kroller-Schon S, Daiber A, Steven S, *et al*. Crucial role for Nox2 and sleep deprivation in aircraft noise-induced vascular and cerebral oxidative stress, inflammation, and gene regulation. *Eur Heart J*. 2018;**39**:3528–3539. doi: 10.1093/eurheartj/ehy333
14. Münzel T, Kröller-Schön S, Oelze M, *et al*. Adverse cardiovascular effects of traffic noise with a focus on nighttime noise and the new WHO noise guidelines. *Annu Rev Public Health*. 2020;**41**:309–328. doi: 10.1146/annurev-publhealth-081519-062400
15. Schmidt FP, Basner M, Kroger G, *et al*. Effect of nighttime aircraft noise exposure on endothelial function and stress hormone release in healthy adults. *Eur Heart J*. 2013;**34**:3508–3514a. doi: 10.1093/eurheartj/eht269
16. Schmidt F, Kolle K, Kreuder K, *et al*. Nighttime aircraft noise impairs endothelial function and increases blood pressure in patients with or at high risk for coronary artery disease. *Clin Res Cardiol*. 2015;**104**:23–30. doi: 10.1007/s00392-014-0751-x
17. Saucy A, Schaffer B, Tangermann L, Vienneau D, Wunderli JM, Roosli M. Does night-time aircraft noise trigger mortality? A case-crossover study on 24 886 cardiovascular deaths. *Eur Heart J*. 2021;**42**:835–843. doi: 10.1093/eurheartj/ehaa957

18. Ellenbogen JM, Kellam CB, Hankard M. Noise-induced sleep disruption from wind turbines: Scientific updates and acoustical standards. *Sleep*. 2024;**47**(2):zsad286. doi: 10.1093/sleep/zsad286
19. Fink D. A new definition of noise: Noise is unwanted and/or harmful sound. Noise is the new 'secondhand smoke'. *Proc Meet Acoust*. 2019;**39**:1–12.
20. Osborne MT, Radfar A, Hassan MZO, *et al*. A neurobiological mechanism linking transportation noise to cardiovascular disease in humans. *Eur Heart J*. 2020;**41**:772–782. doi: 10.1093/eurheartj/ehz820
21. Basner M, Barnett I, Carlin M, *et al*. Effects of aircraft noise on sleep: Federal aviation administration national sleep study protocol. *Int J Environ Res Public Health*. 2023;**20**:7024. doi: 10.3390/ijerph20217024
22. Basner M, Smith MG, Jones CW, *et al*. Associations of bedroom PM(25), CO(2), temperature, humidity, and noise with sleep: An observational actigraphy study. *Sleep Health*. 2023;**9**:253–263. doi: 10.1016/j.sleh.2023.02.010
23. Riedy SM, Smith MG, Rocha S, Basner M. Noise as a sleep aid: A systematic review. *Sleep Med Rev*. 2021;**55**:101385. doi: 10.1016/j.smrv.2020.101385