Transportation noise pollution and cardiovascular disease

Thomas Münzel[1,2] ✉, *Mette Sørensen*[3,4] *and Andreas Daiber*[1,2]

Abstract | Epidemiological studies have found that transportation noise increases the risk of cardiovascular morbidity and mortality, with high-quality evidence for ischaemic heart disease. According to the WHO, ≥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 dysfunction, inflammation and hypertension, thereby elevating the risk of cardiovascular disease. In this Review, we focus on the indirect, non-auditory cardiovascular health effects of transportation noise. We provide an updated overview of epidemiological research on the effects of transportation noise on cardiovascular risk factors and disease, discuss the mechanistic insights from the latest clinical and experimental studies, and propose new risk markers to address noise-induced cardiovascular effects in the general population. We also explain, in detail, the potential effects of noise on alterations of gene networks, epigenetic pathways, gut microbiota, circadian rhythm, signal transduction along the neuronal–cardiovascular axis, oxidative stress, inflammation and metabolism. Lastly, we describe current and future noise-mitigation strategies and evaluate the status of the existing evidence on noise as a cardiovascular risk factor.

Air pollution is an established risk factor for cardiovascular disease (CVD)[1]. Much less attention has been devoted to environmental noise, which co-exists with air pollution mainly in urban areas, although the WHO stated, in their 2018 Environmental Noise Guidelines for the European Region, that high-quality evidence is available to conclude that road traffic noise increases the risk of ischaemic heart disease[2]. Although a large proportion of the general population is exposed to transportation noise levels exceeding the recommended guideline levels, traffic noise is not mentioned or only insufficiently addressed as a risk factor in the Global Burden of Disease (GBD) study[3], the Health at a Glance: Europe 2018 report[4] and in CVD prevention guidelines from the ESC[5] or AHA/ACC[6].

Over the past three decades, the leading causes of the global burden of disease have shifted substantially from communicable diseases to non-communicable diseases, with CVDs caused by atherosclerosis or metabolic disease being the major category (according to data from the GBD study[7], the WHO[8] and the Global Health Observatory[9]). The *Lancet* Commission on pollution and health concluded that "pollution is the largest environmental cause of disease and premature death in the world today" and estimated that pollution accounted for 9 million premature deaths worldwide in 2015, corresponding to 16% of all deaths worldwide[10]. Later estimates indicate that almost 9 million premature global deaths per year are caused by air pollution (particulate matter with a diameter ≤2.5 μm) alone[11,12], mainly on the basis of new evidence showing that even low levels of particulate matter air pollution can increase the risk of death. Although scientific and medical efforts in the past have focused on traditional cardiovascular risk factors (such as diabetes mellitus and smoking)[7], the GBD study suggests that environmental factors have an important role in the development of chronic non-communicable diseases and, therefore, contribute substantially to global mortality[1]. In this context, the concept of the exposome, first described in detail in 2005 by Wild[13], is important. The exposome is the lifelong sum of all the environmental contributions to human physiology and pathophysiology[13] (BOX 1).

Transportation noise is another increasingly recognized environmental pollutant. Transportation noise co-exists with air pollution in urban settings, reflecting that traffic is a major source of both exposures. Historically, noise research focused on the direct adverse health effects of loud noise, typically with a sound pressure level (SPL) of >100 dB(A) but also at lower dB(A) values when exposed chronically, leading to hearing loss (reviewed previously[14]). The first summary of the adverse health effects of non-auditory noise exposure was published in a monography in 1970 and focused on the effects of noise on work performance, sleep, pain,

[1]*Department of Cardiology, Cardiology I, University Medical Center of the Johannes Gutenberg-University, Mainz, Germany.*

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

[3]*Danish Cancer Society, Copenhagen, Denmark.*

[4]*Department of Natural Science and Environment, Roskilde University, Roskilde, Denmark.*

✉*e-mail: tmuenzel@uni-mainz.de*

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Key points

- Noise is associated with cardiovascular diseases, such as arterial hypertension, coronary artery disease, heart failure and arrhythmia, and should therefore be considered a cardiovascular risk factor.
- Noise-induced stress increases blood pressure, stress hormone levels, endothelial dysfunction, oxidative stress, NADPH oxidase 2 (NOX2) activity, nitric oxide synthase uncoupling and vascular inflammation in mice, all of which are prevented by NOX2 deficiency.
- Translational field studies in healthy individuals and patients with heart disease established that short-term simulated aircraft and railway noise impairs sleep quality and increases stress hormone levels, blood pressure, endothelial dysfunction and oxidative stress.
- The quality of evidence on the adverse cardiovascular effects of noise exposure has increased for several cardiometabolic risk factors since the WHO evaluation in 2018, especially for obesity and diabetes mellitus.
- Noise-induced stress increases cerebral oxidative stress and downregulates and uncouples neuronal nitric oxide synthase, providing a potential explanation for the observed retardation in the development of cognitive function (memory and learning) in children exposed to aircraft noise.
- Mitigation strategies to reduce population exposure to transportation noise are available and need to be implemented.

vision and circulation[15] (FIG. 1). A landmark finding from animal studies was the demonstration that noise with a mean SPL of 85 dB(A) increased blood pressure in monkeys by 30 mmHg after chronic exposure to noise[16]. Later studies have confirmed an effect of noise on the cardiovascular system (FIG. 1) through sleep disturbance, annoyance and stress. The long-term exposure to environmental noise is estimated to cause 12,000 premature deaths and 48,000 new cases of ischaemic heart disease per year in Europe[17]. Furthermore, 22.0 million and 6.5 million people are estimated to have chronic high annoyance and chronic high sleep disturbance, respectively, caused by the chronic exposure to noise pollution[17]. These health effects of noise pollution are likely to be underestimated, with new evidence from the WHO demonstrating health effects of noise at levels below the obligatory European Union (EU) Environmental Noise Directive (END) reporting thresholds. In addition, the END does not comprehensively cover all urban areas, roads, railways and airports across Europe[17].

In this Review, we focus on the indirect, non-auditory cardiovascular health effects of transportation noise, including epidemiological and clinical findings and mechanistic and experimental data. We also highlight new risk markers to address noise-induced cardiovascular effects in the general population. Mechanistic data on adverse health effects of noise comprise changes to gene networks, epigenetic pathways, the gut microbiota, circadian rhythm, signal transduction along the neuronal–cardiovascular axis, oxidative stress, inflammation and metabolism. Finally, we provide an outlook on the most promising noise-mitigation strategies and evaluate the current level of evidence on noise as a cardiovascular risk factor.

The cardiovascular effects of noise exposure

Epidemiological evidence

Cardiovascular disease. Environmental noise from roads, railways and aircraft are increasing due to urban growth and increased mobility demands. A mapping of the EU published in 2020 estimated that >113 million people in Europe, corresponding to 20% of the population, are exposed to road traffic noise levels of >55 dB(A) (calculated as the 24-h average sound levels, known as the day–evening–night noise level (L_{den}))[17] (FIG. 2, BOX 2). This number is likely to be markedly underestimated because the EU END does not comprehensively cover all urban areas and/or all roads across Europe[17].

Since the publication in 1988 of the first cohort study of traffic noise and the risk of ischaemic heart disease[18], a number of studies have investigated the association between residential exposure to transportation noise and the risk of CVD, especially during the past decade, resulting in a consolidation of the evidence for transportation noise and CVD[19–23]. In October 2018, the WHO published the Environmental Noise Guidelines for the European Region, in which an expert panel compiled and evaluated the evidence and calculated exposure–response functions for associations between transportation noise and a number of diseases[2]. In these guidelines and in accordance with Grading of Recommendations, Assessment, Development and Evaluation (GRADE), the expert panel concluded that 'high-quality evidence' supported an association between road traffic noise and ischaemic heart disease. Based on meta-analyses, the expert panel calculated that the relative risk of ischaemic heart disease per 10 dB(A) increase in road traffic noise was 1.08 (95% CI 1.01–1.15), starting at 53 dB(A). The expert panel also evaluated rail and aircraft noise in relation to ischaemic heart disease, but the quality of evidence was ranked as very low and low, respectively, owing to no (for rail noise) or few (for aircraft noise) prospective cohort studies. However, two population-based studies in Switzerland and the Rhine-Main region in Germany, respectively, found that railway noise increased the risk of myocardial infarction (MI)[23,24]. For aircraft noise, only the Swiss study observed an increase in the risk of MI, suggesting that these two noise sources are relevant risk factors for MI.

For all other cardiometabolic outcomes evaluated, the WHO expert panel concluded that either very low, low or moderate evidence was available due to the limited number of prospective cohort studies[21]. However, the data collection for the WHO guidelines covered the period from January 2000 to August 2015 and a number of large, prospective studies have subsequently been published[25]. Furthermore, studies published in the past 5 years have suggested that transportation noise could increase the risk of CVDs not previously investigated in a noise context[22,23]. Given the considerable amount of new, well-designed, longitudinal studies, which rank high when evaluating evidence according to GRADE, some of the conclusions in the WHO guidelines need to be updated[25].

For stroke, the WHO expert panel ranked the quality of evidence as moderate[21]. This evaluation was based on five prospective studies: one study on incidence[26], which found that road traffic noise increased the risk of stroke, and four studies on cerebrovascular mortality reporting no association[21,27,28]. Subsequently, four studies on transportation noise and incident stroke have been published. Two large, population-based studies covering a whole

city or region (London and Frankfurt) found that road traffic noise increased the risk of stroke[29,30]. By contrast, smaller, classic cohort studies from Norway, Sweden and the UK with a smaller number of cases (900–1,900) but a more comprehensive adjustment strategy found no association[31,32]. Two large, population-based studies from London and Switzerland have suggested that road traffic noise and, potentially, aircraft noise might increase the risk of stroke-related death, especially from ischaemic stroke[23,30]. Therefore, although large, well-designed prospective studies have added to the evidence base, more longitudinal studies are still needed to clarify to what extent transportation noise affects the risk of stroke and whether noise primarily affects the risk of ischaemic stroke.

Heart failure and atrial fibrillation, two major CVDs, were not evaluated in the WHO guidelines. The effects of transportation noise on the risk of heart failure have been investigated in five longitudinal studies: two classic cohort studies and three population-based studies from London, Switzerland and the Rhine-Main region. These studies consistently reported an association between road traffic, railway and aircraft noise and heart failure incidence and mortality, with a 2–8% increase in risk per 10 dB(A) (REFS[23,27,33–35]). The effects of noise on the risk of atrial fibrillation have been examined only in a few studies, with some indicating a positive association, whereas others report neutral results[22,35,36], emphasizing the need for more studies of noise in relation to this prevalent CVD.

Cardiovascular risk factors. Epidemiological studies have linked transportation noise with a number of cardiovascular risk factors. Some of these were evaluated in the WHO guidelines[2,21]. However, as previously mentioned, the WHO data collection covered the period from January 2000 to August 2015, and subsequent studies have provided new evidence for a link between noise and cardiovascular risk factors and have identified potential risk factors not evaluated by the WHO. In TABLE 1, we list seven important risk factors for CVD potentially associated with road traffic noise. We focus on exposure to road traffic noise because this source has been studied in more depth in relation to cardiovascular risk factors than railway and aircraft noise.

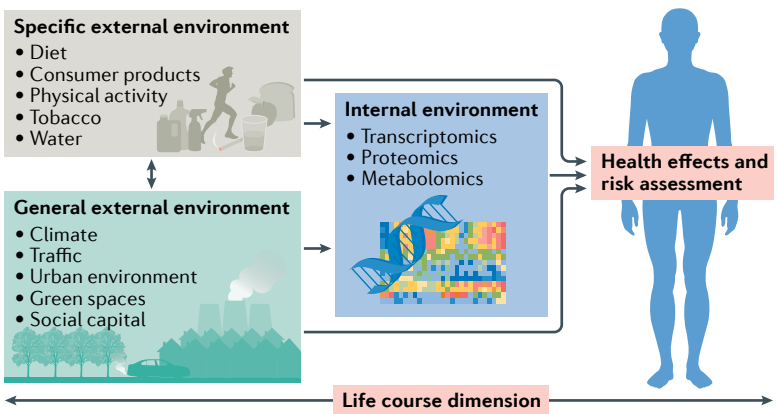
The disturbance of sleep is an important pathway for the harmful effects of noise on the cardiovascular system[37,38]. The WHO expert panel conducted a pooled analysis of polysomnographic studies of the effects of acute noise that showed an increased probability of awakening with road, rail and aircraft noise exposure[39]. Furthermore, night-time noise was associated with being highly sleep disturbed (self-reported) when questions regarding sleep referred to noise, whereas when questions regarding sleep did not refer to noise the associations were smaller and not significant. Two prospective cohort studies on road traffic noise and sleep have since been published: a study of register information on the redemption of sleeping medication showing a weak association with night-time noise >55 dB(A) (REF.[40]) and a study showing an association between being extremely noise annoyed at baseline and self-reported sleep disturbance at follow-up[41]. Therefore, the quality of evidence has increased only slightly since the WHO report, and more studies that use objective indicators or standardized subjective indicators of sleep are needed.

The association between transportation noise and arterial hypertension has been extensively studied[21], although, unfortunately, almost exclusively with cross-sectional approaches. The WHO expert panel found >35 cross-sectional studies on transportation noise and hypertension, with a joint estimate for the relative risk of prevalent hypertension of 1.05 (95% CI 1.02–1.08) per 10 dB(A) increase in L_{den} for road traffic noise[21]. However, the quality of evidence was rated as 'very low' due to the inherent weakness of the cross-sectional design, which limits conclusions on causality. Subsequently, six studies on transportation noise and the risk of incident hypertension have been published, applying different methods of assessing hypertension, ranging from clinical examination and register-based information of prescriptions of antihypertensive medications to self-reported information[35,36,42–45].

Box 1 | The exposome concept

The exposome is the lifelong sum of all the environmental contributors to human physiology and pathophysiology (see the figure). The external exposome is the sum of all environmental exposures, which are subcategorized into the specific and general environments[175]. The specific external environment includes chemical and physical environmental stressors (air, water and soil pollution by chemicals or noise) and behavioural and lifestyle factors (such as diet, smoking, alcohol abuse and physical activity). The general external environment refers to more general environmental factors (such as socioeconomic status, urban environment, pathogens, UV radiation and climate)[159] and includes traffic-dependent noise and air pollution. The internal exposome reflects all biological changes (namely expression levels of biomolecules) that are triggered by environmental factors.

Exposome research is dedicated to identifying the associations between environmental exposures and health effects (such as disease and mortality). Examples of important studies on the associations between environmental exposure or the exposome and health outcomes are the ENNAH, ELAPSE, NordicWelfair/NordSOUND, BREATHE, HELIX, PACE, ESCAPE, HEALS, HERCULES and EXPOsOMICS projects (a detailed list is provided in REF.[165]). All these exposome studies investigate the association between specific environmental exposures and adverse health outcomes and some even have the ambitious aim to identify distinct biochemical signatures (changes in the transcriptome (epigenome), proteome, metabolome or microbiome) that define specific exposures and explain their adverse health effects. More mechanistic insights into the health effects of environmental exposures by exposome projects will be obtained in the future such as from projects funded in the H2020 funding call by the European Union[176]. Figure adapted with permission from BMJ Publishing Group Limited (Vrijheid, M. The exposome: a new paradigm to study the impact of environment on health. *Thorax* **69**, 876–878, https://doi.org/10.1136/thoraxjnl-2013-204949 (2014))[175].



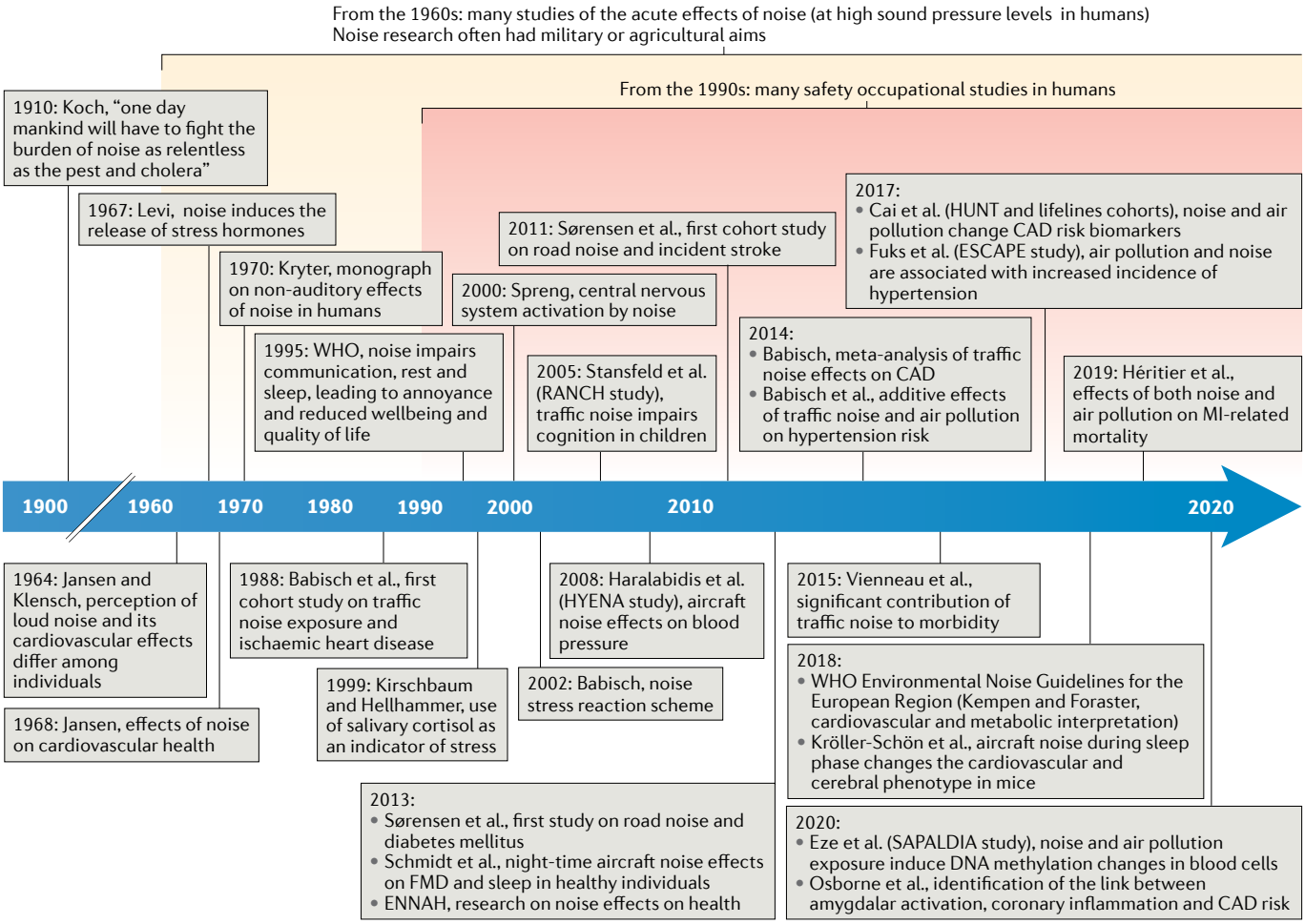


Fig. 1 | **Timeline of research on adverse health effects of noise.** Historical overview of research on the adverse health effects of noise, highlighting important concepts, studies and reports, with a focus on transportation noise. The selection of studies and consortia is based on the authors' personal views of the noise research field. The references to the sources of these important concepts, studies and reports are provided in the Supplementary information. CAD, coronary artery disease; ENNAH, European Network on Noise and Health; FMD, flow-mediated dilatation; MI, myocardial infarction.

However, no clear picture emerges from these new studies, with findings of both positive associations and neutral results. One explanation is that hypertension is a very difficult end point to investigate in a longitudinal design. Studies relying on clinical examinations normally have years between examinations and, therefore, determining when a person develops hypertension might be difficult. Register-based studies relying only on prescriptions of antihypertensive drugs or on self-reported hypertension underestimate the number of cases and, as in studies using clinical examinations, when an individual develops hypertension is largely uncertain. Lastly, studies using self-reported hypertension are often hampered by poor control of antihypertensive drug intake and, additionally, misclassification related to white-coat hypertension is a general problem. Therefore, although the quality of evidence has increased, the inconsistent results and the large between-study variation in the definition of hypertension make drawing conclusions difficult and warrant further studies.

Stress and disturbance of sleep, the two central pathways of the effects of noise on health, are known risk factors for metabolic disease[46,47]. Only one prospective study, showing that road traffic noise increased the risk of diabetes[48], was published at the time of the WHO evaluation and, therefore, the WHO expert panel ranked the quality of evidence as moderate. Since 2017, five new prospective studies point in the same direction, which markedly strengthens the evidence for an association between road traffic noise and diabetes[36,49–52]. The results were combined in a meta-analysis reported in 2019, showing a relative risk of incident diabetes of 1.11 (95% CI 1.08–1.15) per 10 dB(A) L_{den} for road traffic noise exposure and 1.20 (95% CI 0.88–1.63) per 10 dB(A) L_{den} for aircraft noise exposure[53].

At the time of the WHO evaluation, only three cross-sectional studies on the association between road traffic noise and obesity were available, resulting in the conclusion that the quality of evidence was very low[2]. Since then, the evidence base has increased markedly, with four new longitudinal studies on road traffic noise and adiposity in adults[54–57]. Although the markers of obesity varied between the studies, the general conclusion is that road traffic noise is associated

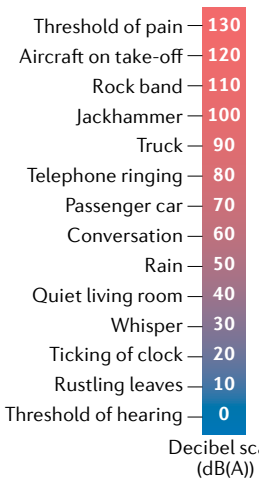
with an increased presence of adiposity markers and obesity. Interestingly, results showing an association with waist circumference and central obesity are more consistent than results on changes in BMI. This finding is in accordance with a noise-induced increase in the stress hormone cortisol, which is expected to result primarily in central obesity. Therefore, future research should include mechanistic studies investigating whether transportation traffic noise exposure increases the risk mainly of central obesity or of general obesity. Additionally, more studies on railway and aircraft noise and obesity are important owing to inconsistent results in available studies[54–60].

Studies published in the past 5 years have indicated that exposure to noise might result in unhealthy behaviours. Two studies on road traffic noise and physical activity found that noise was associated with reduced physical activity[61,62]. Interestingly, the studies indicated that noise mainly affected whether the individual participated in leisure-time sport at all and not the actual time spent playing sport per week. Furthermore, one study on smoking and alcohol consumption found that road traffic noise was positively associated with alcohol consumption and smoking in analyses with a cross-sectional design but not in longitudinal analyses[63]. Therefore, the quality of the evidence for an association between noise and lifestyle risk factors is still low, and more studies are needed to test the hypothesis that transportation noise, through its effect on stress and disturbance of sleep, leads to an unhealthy lifestyle.

A link between transportation noise and depression has been suggested, but the WHO expert panel concluded that the quality of evidence was very low[64]. Subsequently, four longitudinal studies have been conducted, all suggesting an association between road traffic noise and the risk of depression[41,65–67]. In addition, a 2020 update concluded that the quality of evidence increased to 'low' for the association between road traffic noise exposure and an increased risk of antidepressant use and interview-based measures of depression[68]. A major problem is that studies on depression apply a broad range of definitions of depression, ranging from interview-based measures, intake of antidepressants and hospital admissions to self-reported depression, making the comparison between studies difficult. Therefore, more longitudinal studies investigating standardized definitions of depression are needed.

Estimation of transportation noise in epidemiological studies. Most of the latest epidemiological studies use source-propagation noise models to estimate noise exposure at defined building facade points. The gold standard is to use the exact addresses. However, some studies have only area-level information on place of residence, such as the postal codes[30], and estimate noise at the centre of such an area. Other studies use noise maps, assigning noise levels on the basis of the grid cell in which the address is located[69]. These approaches have a high risk of exposure misclassification, which has been found to result in attenuation of the risk estimate[70]. Furthermore, input variables and model settings vary widely from study to study, for example, with regard to screening (accounting for the screening from terrain, buildings and noise screens), the quality of traffic information (for example, inclusion of information from smaller roads) and the number of reflections included. All this information has to be considered when evaluating the quality of the exposure assessment.

a SPL of noise sources



b 2018 WHO Environmental Noise Guidelines

c Adverse health effects of noise exposure

Chronic noise exposure	Adverse health effects	Noise source	Association	Participants (*n*)	Events (*n*)	Quality level of evidence
L_{den} >45 dB(A) for aircraft noise L_{den} >54 dB(A) for road and railway noise	Stroke	Road	Incidence	51,485	1,881	+++
			Mortality	581,517	2,634	+++
		Aircraft	Incidence	>9 million	97,949	+
			Mortality	>4 million	25,231	+++
	Coronary artery disease	Road	Incidence	67,224	7,033	++++
			Mortality	532,268	6,884	+++
		Aircraft	Incidence	>9 million	158,977	+
			Mortality	>4 million	15,532	++
	Depression	Road	Incidence	>1.2 million	–	+++
	Anxiety	Road	Incidence	372,079	–	+++
L_{night} >40–42 dB(A)	Sleep disturbance					

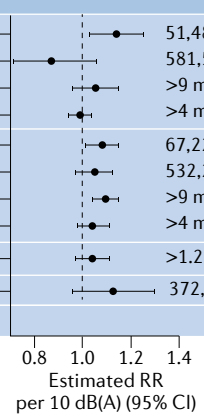


Fig. 2 | **Noise sources and levels and their adverse health effects based on epidemiological data. a** | Sound pressure levels (SPLs) of different noise sources[72]. **b** | According to the 2018 WHO Environmental Noise Guidelines for the European Region[21], the non-auditory adverse health effects of noise, such as psychological, cardiovascular and cerebrovascular diseases, are initiated by chronic exposure to L_{den} (day–evening–night noise level) of 45–54 dB(A). Adverse effects of noise on sleep are observed in response to L_{night} (A-weighted equivalent noise level for the night period) of 40–42 dB(A). **c** | The incidence of stroke, coronary artery disease, depression and anxiety increases in response to chronic exposure to road or aircraft noise (expressed as relative risk (RR) estimates for every 10 dB(A) increase in exposure). Noise exposure is associated with an increased risk of death from coronary artery disease but not from stroke. Generated from data summarized in the 2018 WHO Environmental Noise Guidelines by Kempen et al. for stroke and coronary artery disease[21] and by Dzhambov et al. for psychological disease[171]. +, very low; ++, low; +++, moderate; ++++, high. Panel **a** adapted with permission from REF.[172], Oxford University Press.

Box 2 | **Noise research terms**

- The sound pressure level is mostly expressed using the logarithmic decibel (dB(A)) scale. The A-weighting is used to account for the varying sensitivity of the human ear at different sound frequencies (such as reduced sensitivity for low audio frequencies). The Decibel A-weighted value compensates for this variation in the human hearing sensitivity and most commercial acoustic measurement devices express the sound pressure level as dB(A).
- L_{Aeq}, the energy-equivalent average A-weighted sound pressure level expressed in decibels, is the most commonly used noise-exposure metric reflecting (energetically) averaged noise exposure over a certain time period. The A-weighting accounts for the varying sensitivity of the human ear at different sound frequencies. The duration of the averaging period within the 24 h is often amended (such as L_{Aeq}16 h, usually reflecting the period from 0700 to 2300 hours). The L_{Aeq} is often calculated for long periods (such as over 1 year or the busiest 6 months of the year).
- L_{den}, the day–evening–night noise level, is the 24-h average sound pressure level calculated for an annual period but with a 5 dB(A) penalty for evening and a 10 dB(A) penalty for night. The penalties are introduced to indicate people's extra sensitivity to noise during the evening and the night. With respect to long-term health effects, these metrics are calculated as average annual exposure indicators.
- L_{night} is the L_{Aeq} for the night period (usually from 2300 to 0700 hours).

Mechanisms

The noise effects reaction scheme. Babisch introduced the noise reaction model, in which a so called 'indirect pathway' has a central role in the development and progression of CVD[71] (FIG. 3a). An important process in this model is the cognitive perception of noise, which triggers cortical activation and the release of stress hormones that, in the long run, might lead to the manifestation of cardiovascular risk factors, such as diabetes, high plasma cholesterol levels and high blood pressure, and subsequently to CVD (such as MI, heart failure, persistent hypertension, arrhythmia and stroke)[19,72]. Furthermore, noise disturbs sleep, activities and communication, which might lead to annoyance and increased risk of CVD (in particular ischaemic heart disease[73]) and arrhythmia such as atrial fibrillation[74].

The noise-induced activation of the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system (SNS) leads to the release of stress hormones, such as cortisol and catecholamines, and subsequently to the induction of inflammation (with increases in the circulating levels of IL-1β, IL-6 and pro-inflammatory monocytes[75,76]) and oxidative stress[38,77,78]. Night-time aircraft noise exposure has been associated with stress-induced cardiomyopathy (also known as Takotsubo syndrome)[79]. Stress reactions, including higher glucocorticoid and catecholamine levels, lead to higher blood pressure, which can impair the function of endothelial nitric oxide synthase (NOS) and increase oxidative stress in the vasculature, thereby reducing vascular NO bioavailability. All these alterations lead to endothelial dysfunction[80] and to a supersensitivity of the vessels to stress hormone-induced vasoconstriction[81]. The underlying mechanisms of noise-induced stress reactions and the development of cerebrovascular inflammation and oxidative stress are summarized in FIG. 3 (reviewed previously[76,77]).

A study published in 2020 showed that the amygdala, which is part of the limbic system and is involved in stress perception and control of emotions, provides a 'cerebral' link between a noise stimulus, vascular inflammation and major adverse cardiovascular events (MACE)[82]. In this study, 498 adults without CVD or active cancer underwent clinical ^{18}F-fluorodeoxyglucose PET–CT imaging to quantify amygdalar metabolic activity and the degree of arterial (aortic) inflammation. A higher noise exposure was associated with increased amygdalar activity and vascular inflammation and a higher risk of MACE (HR 1.341, 95% CI 1.147–1.567, per 5 dB(A) increase), which remained robust after common multivariable adjustments. Mediation analysis indicated that a higher noise exposure was associated with MACE via a serial mechanism involving heightened amygdalar activity and arterial inflammation[82,83].

Cardiovascular effects of noise exposure in humans. Mechanistic studies of the cardiovascular health effects of noise exposure in humans date back to the 1960s. Noise exposure was shown to induce vasoconstriction of peripheral blood vessels in individuals performing exercise[84]. Another study found that individuals exposed to noise or music had various haemodynamic responses (in cardiac output and minute flow), and the investigators concluded that sound intensity and not its aversive (noise) or its pleasurable (music) aspects controlled the somatic responses[85]. According to a study in 1,005 German industrial workers, peripheral circulation problems, heart problems and disturbances in the sense of balance were more pronounced in individuals working in very noisy industries than in those working in less noisy industries[86]. The Speedwell study[87] reported significant associations between noise (average SPL (L_{eq}) 51–70 dB(A) for 6–22 h) and potential risk factors for ischaemic heart disease, including total plasma triglyceride levels, platelet count, plasma viscosity, blood glucose levels (increases), and systolic and diastolic blood pressure. Higher levels of noise exposure are significantly associated with higher systolic and diastolic blood pressure as well as heart rate[88]. Independent studies reported that exposure to night-time transportation noise is associated with more pronounced increases in blood pressure than exposure during the daytime[69,89] and that repeated night-time autonomic disturbances probably interfere with blood-pressure dipping[90]. Individuals exposed to high levels of noise (workers of a starch factory; energy-equivalent average A-weighted SPL (L_{Aeq}) >80 dB(A)) had significantly higher glutathione peroxidase levels, systolic and diastolic blood pressure, and DNA damage (measured by the comet assay) than individuals exposed to low levels of noise (office workers, L_{Aeq} 40–50 dB(A))[91].

In a series of field studies, our group investigated the adverse effects of aircraft and railway noise on vascular (endothelial) function, sleep quality, stress hormone release and markers of inflammation in healthy individuals and patients with established coronary artery disease (CAD). These studies showed that night-time aircraft noise exposure (L_{eq} 46.3 dB(A), peak level 60 dB(A) for 1 night) reduced sleep quality, increased stress hormone levels, caused endothelial dysfunction (a subclinical parameter for atherosclerosis) and decreased pulse transit time (indicating SNS activation) in healthy

Table 1 | **Epidemiological studies on road traffic noise and cardiovascular risk factors**

Conclusions in the 2018 WHO guidelines[2,21,39,64a]	Prospective case–control and cohort studies not included in the 2018 WHO guidelines[b]		Updated conclusions
	Design	Results	
Sleep disturbance			
Moderate quality of evidence; percentage of highly sleep-disturbed persons (self-reported) for L_{night} OR 2.13 (95% CI 1.82–2.48) for questionnaires referring to noise and OR 1.09 (95% CI 0.94–1.27) for questionnaires not mentioning noise; probability of awakening for indoor L_{max} (polysomnographic studies) OR 1.36 (95% CI 1.19–1.55)	Cohort study, Denmark, *n* = 44,438	HR for redemption of sleep medication 1.02 (95% CI 0.98–1.07) for 45–50 dB(A), 1.01 (95% CI 0.99–1.03) for 50–55 dB(A) and 1.05 (95% CI 1.00–1.10) for >55 dB(A) per 10 dB(A) increase in 10-year mean L_{night} (reference <45 dB(A))[40]	The quality of evidence has increased only slightly; more studies using objective indicators or standardized subjective indicators of sleep and a longitudinal approach are needed to increase the quality of evidence
	Cohort study, Germany, *n* = 9,354	RR 1.19 (95% CI 1.10–1.28) for self-reported sleep disturbance at follow-up for people reporting to be extremely annoyed by road traffic noise at night at baseline[41]	
	Review of cross-sectional studies	For road traffic noise and sleep "no large differences are expected" compared with the evaluation in the WHO guidelines[25]	
Hypertension			
Low-quality evidence for RR incidence (0.97, 95% CI 0.90–1.05); only one cohort study; very low-quality evidence for RR prevalence (1.05, 95% CI 1.02–1.08)	Cohort study, Greece, *n* = 71	OR 1.18 (95% CI 0.92–1.52) per 10 dB(A) L_{Aeq}[36]	The quality of evidence has increased, with six new prospective studies, which found either weak or no association with hypertension; however, large between-study variation exists in the definition of hypertension and more studies are needed to examine whether road traffic noise leads to hypertension
	Cohort study, Sweden, *n* = 1,386	HR 0.93 (95% CI 0.86–1.01)[45]	
	Case–control study, Germany, *n* = 137,577	OR 1.00 (95% CI 0.99–1.01)[44]	
	Cohort study, UK, *n* = 17,785	HR 1.01 (95% CI 0.94–1.08) for 55–60 dB(A) and 0.99 (95% CI 0.88–1.05) for >60 dB(A) L_{night} (reference <55 dB(A))[35]	
	Cohort study, pooled analyses from 4–6 European cohorts, *n* = 6,207 for self-reported and *n* = 3,549 for 'measured' incident	RR 1.03 (0.99–1.07) for self-reported hypertension, RR 0.99 (0.94–1.04) for measured hypertension[42]	
	Cohort study, Denmark, *n* = 21,241	HR 1.00 (95% CI 0.98–1.02)[43]	
Diabetes mellitus			
Moderate-quality evidence RR for incidence (1.08, 95% CI 1.02–1.14); only one cohort study	Cohort study, Canada, *n* = 12,941	OR 1.11 (95% CI 1.06–1.15)[49]	The quality of evidence has increased, with five new prospective studies, which fairly consistently found that road traffic noise increased the risk of diabetes
	Cohort study, Greece, *n* = 30	OR 1.18 (95% CI 0.85–1.65)[36]	
	Cohort study, Switzerland, *n* = 110	RR 1.38 (95% CI 1.04–1.84)[50]	
	Cohort study, Germany, *n* = 330	RR 1.11 (95% CI 0.97–1.27)[51]	
	Cohort study, Denmark, *n* = 1,158	HR 1.03 (95% CI 0.87–1.22) for 48–58 dB(A) and 1.08 (95% CI 0.89–1.31) for >58 dB(A) (reference <48 dB(A))[52]	
	A meta-analysis including five of the six current studies on diabetes incidence	RR of 1.11 (95% CI 1.08–1.15) for road traffic noise[53]	
Obesity			
Very low-quality evidence; change in BMI 0.03 kg/m^2 (–0.10 to 1.15 kg/m^2), change in waist circumference 0.17 cm (–0.06 to 0.40 cm); three cross-sectional studies	Cohort study, Denmark, *n* = 39,720	Yearly weight gain 15.4 g (2.1–28.7 g), yearly increase in waist circumference 0.22 mm (0.02–0.43 mm), RR for gaining >5 kg during follow-up 1.10 (95% CI 1.04–1.15)[56]	The quality of evidence has increased considerably since the WHO guidelines (which relied only on cross-sectional studies), with four new prospective studies, which fairly consistently found that road traffic noise was associated with obesity, most consistently with an increase in waist circumference (central obesity)
	Cohort study, Sweden, *n* = 5,712	Yearly weight gain 10 g (–9 to 30 g), yearly increase in waist circumference 0.4 mm (0.2–0.6 mm)[54]	
	Cohort study, Switzerland, *n* = 3,796	Change in BMI –0.04 kg/m^2 (–0.13 to 0.06 kg/m^2); RR for developing obesity 1.25 (95% CI 1.04–1.51)[55]	
	Cohort study, Denmark, *n* = 52,661 pregnant women	Postpartum weight retention (18 months after pregnancy) 90 g (2–160 g)[57]	

Table 1 (cont.) | **Epidemiological studies on road traffic noise and cardiovascular risk factors**

Conclusions in the 2018 WHO guidelines[2,21,39,64a]	Prospective case–control and cohort studies not included in the 2018 WHO guidelines[b]		Updated conclusions
	Design	Results	
Physical activity			
Not evaluated	Cohort study, Denmark, $n = 39,725$	OR 1.12 (95% CI 1.07–1.18) for ceasing leisure-time sport, OR 0.92 (95% CI 0.87–0.96) for initiating leisure-time sport[62]	Low-to-moderate quality of evidence; two longitudinal studies found that road traffic noise was negatively associated with leisure-time sport; more studies are needed
	Cohort study, Switzerland, $n = 3,842$	OR 0.97 (95% CI 0.94–0.98) for starting moderate physical activity (compared with inactive) per one noise-annoyance rating point[61]	
Smoking and alcohol consumption			
Not evaluated	Cohort study, Denmark, $n = 43,090$	Change in smoking intensity during follow-up 0.03 g per day (–0.20 to 0.26 g per day), change in alcohol consumption during follow-up 0.01 g per day (–0.23 to 0.24 g per day); cross-sectional findings: road traffic noise was positively associated with baseline alcohol consumption (adjusted difference 1.38 g per day, 95% CI 1.10–1.65) and smoking intensity (adjusted difference 0.40 g per day, 95% CI 0.19–0.61)[63]	Very low quality of evidence; uncertainty remains about whether noise exposure increases smoking and alcohol consumption; more longitudinal studies needed
Depression			
Very low-quality evidence; no effect indicated on medication intake for treatment of anxiety and depression and for self-reported depression, anxiety and psychological symptoms; interview measures of depressive and anxiety disorders	Case–control study, Germany, $n = 77,295$	OR 1.17 (95% CI 1.10–1.25) for redemption of antidepressants[67]	An increase to low-quality evidence as shown in an updated evaluation conducted by members of the 2018 WHO guideline group[68]
	Cohort study, Germany, $n = 302$	RR 1.29 (95% CI 1.03–1.62) for >55 dB(A) versus ≤55 dB(A) for depression defined based on depressive symptoms (standardized scale) and antidepressant intake[66]	
	Cohort study, Canada, $n = 140,456$	HR 1.32 (95% CI 1.08–1.63) for 60 dB(A) versus 50 dB(A) L_{night} (combined estimate of road, rail and aircraft noise) for risk of hospitalization for postpartum depression[65]	
	Cohort study, Germany, $n = 9,354$	RR 1.28 (95% CI 1.13–1.46) for self-reported depression at follow-up for people reporting to be extremely annoyed by road traffic noise at night at baseline[41]	

All estimates given per 10 dB(A) increase in noise exposure unless otherwise stated. L_{Aeq}, energy-equivalent average A-weighted sound pressure level; L_{max}, maximum noise level; L_{night}, A-weighted equivalent noise level during the night period. [a]Conclusions in the WHO guidelines are based on the Grading of Recommendations Assessment, Development and Evaluation system, which categorizes the quality of evidence into very low (defined as "any estimate of effect is very uncertain"), low (defined as "further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate"), moderate (defined as "further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate") and high (defined as "further research is unlikely to change our confidence on the estimate of effect"). [b]Identification of the studies was conducted in PubMed, reference lists in articles found in PubMed and the authors' knowledge of the noise research field.

individuals[38] (FIG. 4). Interestingly, in a subgroup of six healthy participants, endothelial dysfunction was reversed by the acute administration of vitamin C, indicating the involvement of reactive oxygen species (ROS) in causing the vascular dysfunction[38]. The adverse effects of aircraft noise on endothelial function were most pronounced in patients with established CAD, indicating that an already damaged endothelium is more susceptible to further deterioration[72,92]. Similarly, exposing healthy individuals to 30 train events or 60 train events during the night-time (average night SPL 52 dB(A) and 54 dB(A), respectively) decreased the quality of sleep and significantly impaired flow-mediated dilatation of the brachial artery compared with control individuals exposed to background noise (average night SPL 33 dB(A))[93]. The acute administration of vitamin C significantly improved the railway noise-induced endothelial dysfunction. Targeted proteomic analysis of plasma proteins showed significant alterations in redox, prothrombotic and pro-inflammatory pathways in the individuals exposed to train noise[93].

Our group also investigated the effect of loudness and frequency of a noise event on endothelial function by exposing patients with established CAD to two night-time aircraft noise scenarios with the same L_{eq} (45 dB(A) for 1 night), consisting of either a few loud noise events or more frequent quieter noise events[94]. The two scenarios resulted in a similar worsening of endothelial

function (measured by flow-mediated dilatation) and diastolic heart function (assessed by serial echocardiography) compared with the control group (L_{eq} 37 dB(A)). The exploratory protein analysis (proximity extension assay) revealed reduced levels of three biomarkers (follistatin, glyoxalase I and angiotensin-converting enzyme 2) involved in the regulation of heart function, oxidative stress, inflammation and fibrosis.

Cross-sectional cohort studies showed that exposure to traffic noise affects the immune system, such as increasing IL-12 and high-sensitivity C-reactive protein (hsCRP) levels and decreasing natural killer cell populations and activity[95,96]. However, these results are not consistent in all field studies[97]. These alterations have been shown to be associated with increased circulating cortisol levels and noise sensitivity[95,96]. Interestingly, the Swiss cohort study SAPALDIA[98] found that long-term exposure to source-specific transportation noise and air pollution was associated with mutually independent DNA methylation patterns, with distinct and shared enrichments in pathways related to inflammation, cellular development and immune responses. The SAPALDIA consortium also reported that chronic exposure to nocturnal intermittent train or road traffic noise induces arterial stiffness as determined by pulse wave velocity[99]. In support of this finding, a German cohort study found that long-term exposure to night-time traffic noise was associated with subclinical atherosclerosis[100], especially in participants with early arterial calcification[101]. These data fit with the concept that noise exposure is associated with elevated stress hormone levels, increased recruitment and/or activation of immune cells, and impaired cardiovascular function. Importantly, the highest cardiovascular event rates were associated with the most pronounced immunological changes[102,103].

In summary, these data provide pathophysiological and molecular evidence from studies in humans that explain, at least in part, the increased incidence of CVD with exposure to noise. Importantly, the experimental data in humans (such as increases in stress pathways, inflammation, oxidative stress, parameters of arterial stiffness, and endothelial and cardiac dysfunction) correlate with mechanistic data from animal models (including next-generation sequencing data), as discussed in the subsequent sections.

Cardiovascular effects of noise exposure in animals. Chronic noise exposure causes a sustained increase in blood pressure in monkeys (industrial noise with L_{eq} 85 dB(A) and peak SPL 97 dB(A) for 9 months)[16] and rats (audiogenic stress with 85 dB(A), 12 h per day for 8 weeks; 95 dB(A), 16 h per day for 4 weeks)[104]. Importantly, in most experimental studies, the SPLs used were very high, even exceeding 100 dB(A). Animal studies

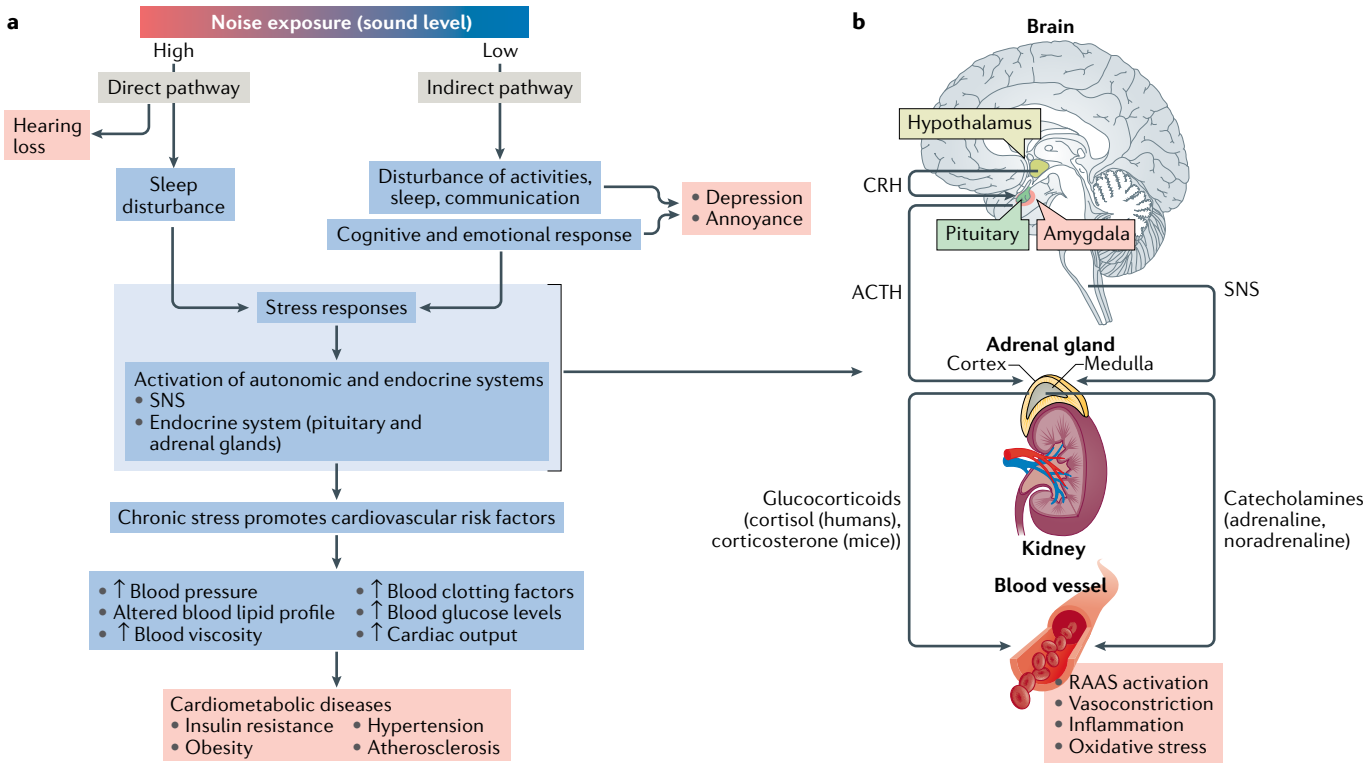


Fig. 3 | **Noise–stress concept and the adverse health consequences in humans. a** | Noise reaction model for the direct (auditory) and indirect (non-auditory) effects of noise exposure[173]. **b** | Neuronal activation (arousals) induced, for example, by noise exposure triggers signalling via the hypothalamic–pituitary–adrenal axis and sympathetic nervous system (SNS). In the hypothalamic–pituitary–adrenal axis, the hypothalamus releases corticotropin-releasing hormone (CRH; also known as corticoliberin) 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 neurohormonal pathways (such as the renin–angiotensin–aldosterone (RAAS) system) and to increased inflammation and oxidative stress, which can ultimately have adverse effects on cardiovascular function and molecular targets. Panel **a** reprinted with permission from REF.[173], Oxford University Press.

addressing the cardiovascular effects (including endothelial dysfunction) of lower noise levels (<100 dB(A)) other than changes in blood pressure are rare. For example, in rats, exposure to white noise for 2 weeks and 4 weeks (100 dB(A), 4 h per day, 6 days per week) caused impaired endothelium-dependent vasodilatation of the thoracic aorta, a higher sensitivity to the vasoconstrictor serotonin and an increase in systolic blood pressure by 31 mmHg (REF.[105]). A study using a similar noise-exposure protocol showed an increased systolic blood pressure in rats after 3 weeks (by 25 mmHg) and 4 weeks (by 37 mmHg) of noise exposure and endothelial dysfunction in isolated mesenteric artery rings from these animals[106]. Rats exposed to white noise levels of ≥100 dB(A) have more pronounced oxidative DNA damage (detected by the comet assay) in the heart and adrenal gland than rats exposed to maximal 30 dB(A) background noise[107,108]. A growing body of evidence suggests that the background noise level (starting at 42 dB(A) with peak levels at 60–70 dB(A)) in animal housing units can induce substantial pathophysiological changes, including increased blood pressure and stress hormone levels, vascular dysfunction, immunomodulation, slower wound healing, weight loss, and impaired fertility and reproduction[109].

The exposure of rats to white noise (90 dB(A), 15 min daily for 3 weeks) induces mesenteric microvascular structural damage with an increased number of leaks, which was significantly reduced by co-treatment with anti-inflammatory and antioxidant agents[110]. The exposure of mice to high-decibel levels (119 dB(A)) reduces blood flow in the cochlea[111]. Loud noise (100–120 dB(A)) has also been shown to activate SHC-transforming protein 1 (SHC1, also known as p66^{Shc}; a mitochondrial source of oxidative stress) in the cochlea, leading to cochlear vascular dysfunction and transient noise-induced hearing loss[112]. This process is associated with higher levels of markers of oxidative stress, inflammation and ischaemia, all of which were prevented by *Shc1* deletion. The exposure of rats to infrasound (120 dB(A)) induces coronary perivascular fibrosis[113]. Exposing pigs to low-frequency but high-intensity noise (140 dB(A)) induces a high permeability of the blood–brain barrier due to leaky tight junctions[114].

Our group established an animal model to investigate the effects of aircraft noise on cardiovascular biomarkers by exposing mice to around-the-clock aircraft noise (L_{eq} 72 dB(A), peak level 85 dB(A) for 24 h for 1, 2 or 4 days). This protocol resulted in a significant increase in stress hormone levels, blood pressure, vascular and cerebral oxidative stress (mainly originating from the activity of NADPH oxidase 2 (NOX2) and uncoupled NOS) and inflammation (caused by infiltrating immune cells) (FIG. 5). Importantly, mice exposed to white noise (similar exposure time and mean SPL) did not show these cardiovascular effects, implying that noise characteristics (such as frequency or pattern) rather than the SPL determine the extent of cardiovascular damage[78]. RNA-sequencing analysis revealed a dysregulation of gene networks in response to noise, identifying potential noise-related

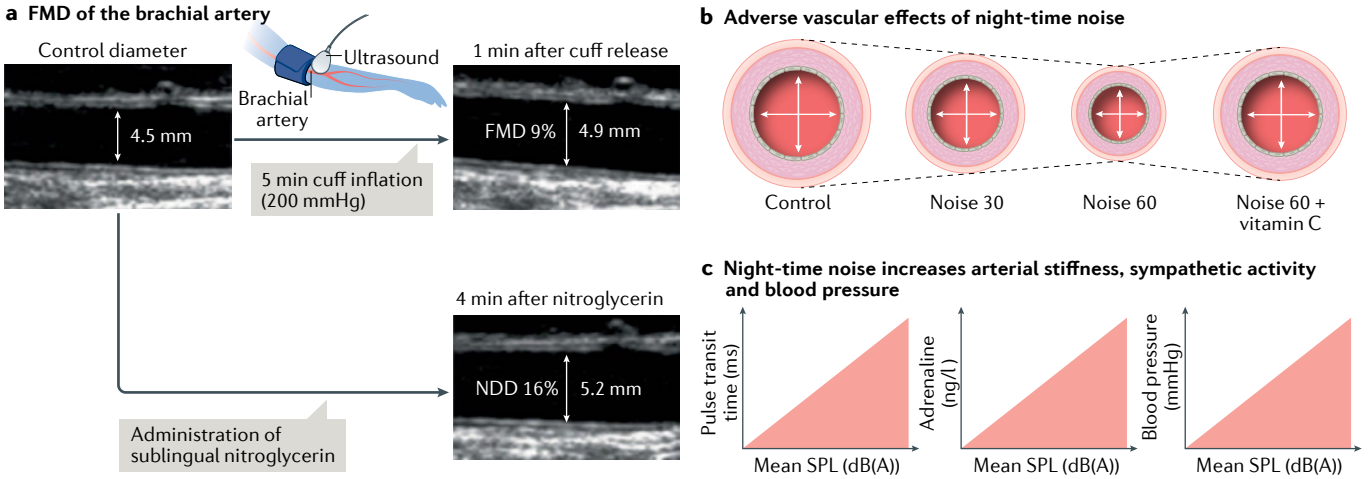


Fig. 4 | **Adverse health effects of night-time noise in humans.** The health effects of exposure to transportation noise in humans based on findings from interventional field studies. **a** | Methodology to determine endothelial function with the flow-mediated dilatation (FMD) technique. Following the measurement of baseline brachial artery diameter, a blood-pressure cuff is inflated for 5 min to suprasystolic blood-pressure levels to stop forearm blood circulation. The release of the cuff after 5 min causes a strong reactive hyperaemia and increased forearm blood flow and thereby increased shear stress on endothelial cells, which results in an endothelium-dependent vasodilatation that is largely dependent on the release of endothelium-derived nitric oxide. FMD is measured by high-resolution B-mode ultrasonography. FMD changes with age (as a result of increasing vascular stiffness); therefore, the maximal diameter of the vessel needs to be determined for normalization of the FMD value. For this purpose, the maximal vasodilatation in response to sublingual nitroglycerin administration is measured. **b** | Schematic representation of the adverse effects of simulated night-time aircraft or train noise (30 (noise 30) or 60 (noise 60) noise events) on FMD of the brachial artery in response to post-ischaemic hyperaemia compared with exposure to background noise (control) and the beneficial acute effects of administration of the antioxidant vitamin C[38,93]. **c** | Exposure to night-time noise increases arterial stiffness (assessed by decreased pulse transit time), sympathetic activation (assessed by circulating adrenaline levels) and blood pressure[38,92]. NDD, nitroglycerin-dependent dilatation; SPL, sound pressure level. Imaging panels in part **a** adapted with permission from REF.[174], © Georg Thieme Verlag KG.

risk marker genes in the vasculature, including genes related to impaired endothelial and vascular signalling[78]. The four most upregulated genes in aortic tissue from noise-exposed animals compared with control animals were *Zbtb44*, *Ypel2*, *Setad4* and *Ihh* (which encode a protein with a zinc-finger domain DNA-binding site, a protein involved in transcription and central phosphatase signalling, a protein residing predominantly in the nucleus and a protein involved in kinase pathways, respectively). The most downregulated genes were *Sacs*, *Nbeal1*, *Nr4a3* and *Ptpn4* (encoding proteins involved in TGFβ signalling, autophagy, matrix metalloproteinase regulation and fibrosis, and cell growth, respectively). Cellular pathway analysis identified changes in NF-κB and adrenergic signalling, focal adhesion, cell cycle control, apoptosis, and growth and proliferation kinase-mediated signalling, with FOXO transcription factors as central mediators. Aircraft noise exposure also modulated the signalling pathways related to circadian rhythm, insulin and calcineurin[78]. Importantly, aircraft noise exposure during sleep was substantially more detrimental to the cardiovascular system than exposure during the awake phase, mediated by triggering endothelial dysfunction, increases in blood pressure, increases in the circulating levels of neurohormones and oxidative stress in the vasculature and the brain, as well as dysregulation of FOXO3 and circadian clock signalling (as identified by next-generation RNA sequencing)[115]. Of note, aircraft noise-induced vascular and cerebral damage was almost completely prevented by *Nox2* deletion, pointing to the crucial role of inflammatory cells in mediating the noise-induced cardiovascular and cerebral effects. Aircraft noise also induced the downregulation and uncoupling of neuronal NOS, triggering a neuroinflammatory phenotype (as shown by the presence of markers of inflammation and astrocyte activation) with increased ROS formation in the brain (FIG. 5). All these effects might explain, at least in part, the decreased cognitive development in the areas of learning and memory observed in children exposed to aircraft noise[115].

Interestingly, the molecular mechanisms of vascular dysfunction in response to around-the-clock and night-time aircraft noise, mediated by inducing oxidative stress and inflammation, are strikingly similar to the mechanisms by which traditional cardiovascular risk factors, such as diabetes[116], hypertension[117], hypercholesterolaemia[118] and smoking[119], induce endothelial and vascular dysfunction. The shared pathological mechanisms suggest that noise-induced stress combined with existing cardiovascular risk factors might result in a markedly accelerated process of vascular and cerebral atherosclerosis and neurodegenerative disease. Accordingly, we observed that the adverse cardiovascular effects of aircraft noise were exacerbated in mice with existing arterial hypertension (L_{eq} 72 dB(A), peak SPL 85 dB(A) for 24 h for 7 days)[120]. This phenomenon is mainly triggered by higher increases in blood pressure, vascular inflammation and oxidative stress. Noise exposure also potentiates neuroinflammation and cerebral oxidative stress in animals with pre-existing hypertension[120]. Noise exposure (mean SPL 72 dB(A) for 4 days) also led to impaired DNA-repair capacity, as shown by increased oxidative DNA damage (8-oxoguanine) and NOX2 expression, in C57BL/6 mice, with synergistic increases with 8-oxoguanine DNA glycosylase deficiency[121]. Noise exposure and deficiency in 8-oxoguanine DNA glycosylase also had additive effects on the degree of oxidative burst of blood leukocytes, other markers of oxidative stress and inflammation[121].

Neuroendocrine effects of noise exposure in animals. The molecular links between noise-induced stress (hypothalamic–pituitary–adrenal axis, SNS and renin–angiotensin–aldosterone system (RAAS) activation) and the induction of vascular and cerebral inflammation and oxidative stress are illustrated in FIGS 3 and 5 (reviewed previously[77,122]). Acute noise exposure for 30 min (85 dB(A)) increases the levels of the adrenocorticotropic hormone corticosterone in a dose-dependent manner[123,124]. In rats, chronic noise exposure upregulated *Crh* and *Crhr1* mRNA levels in the amygdala[125]. The exposure of rats to moderate noise (SPL 70 or 85 dB(A), 8–16 kHz, 6 h per day for 3 months) caused neuroendocrine modulation, with increased corticosterone and lipid peroxidation levels being more pronounced in the 85 dB(A) group[126]. These effects were associated with morphological changes in the heart, with inflamed areas of the pericardium and dilated veins following exposure to 70 dB(A) and more dilated veins in the periphery of the pericardium following exposure to 85 dB(A). Noise exposure (octave band noise 80–100 dB(A), 8–16 kHz, 8 h per day for 20 days) in rats adversely affects the cardiovascular system by increasing the levels of circulating stress hormones (such as corticosterone, adrenaline, noradrenaline and endothelin 1) and the levels of the oxidative stress marker malondialdehyde[127]. Noise exposure also increased heart rate, mean arterial blood pressure and circulating levels of nitrogen oxides, a marker of nitric oxide generated by inducible NOS in inflammatory cells.

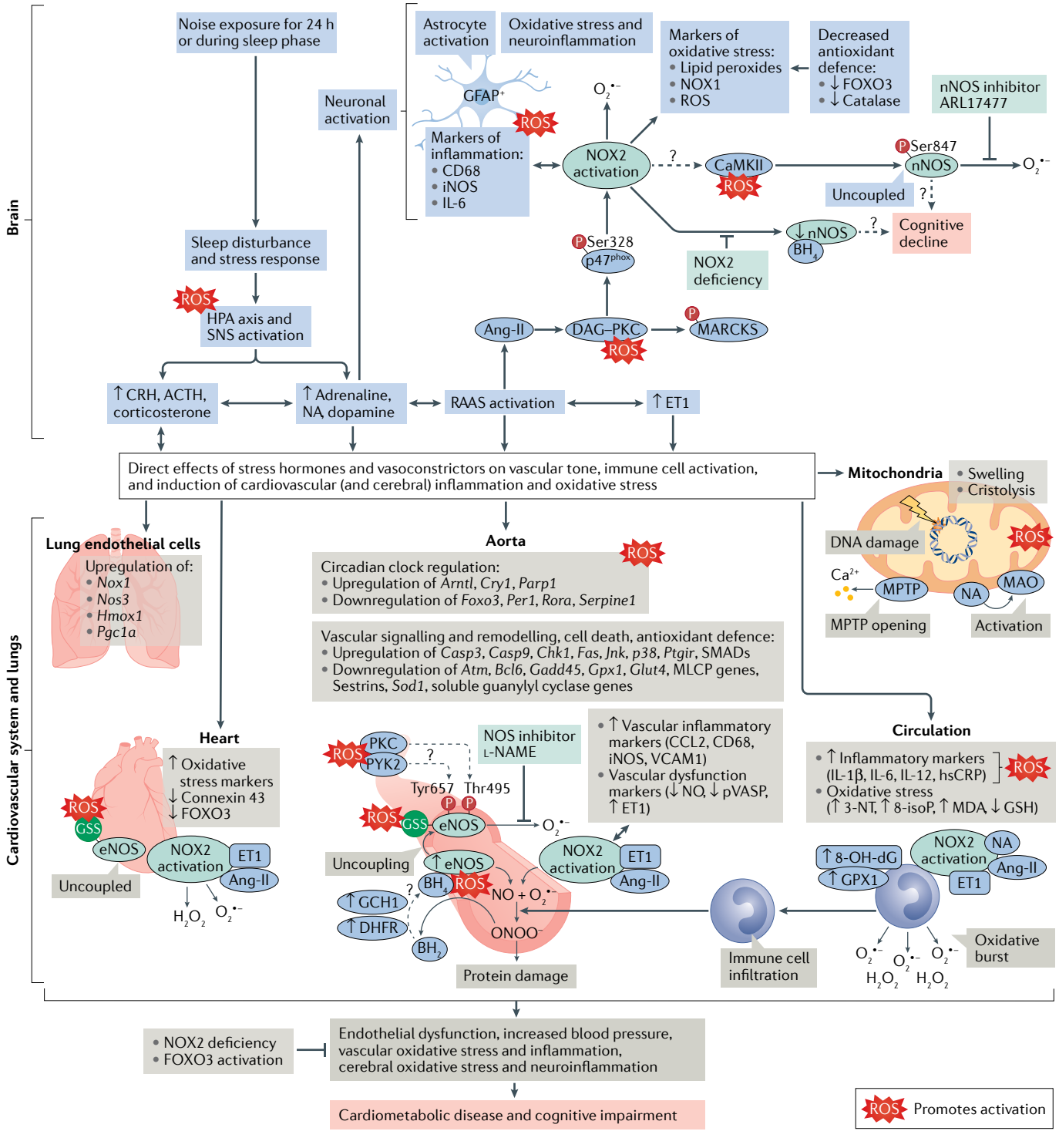
The crosstalk between stress hormones and vasoconstrictors provides a direct explanation for the observed dysregulation of vascular tone in response to noise (FIGS 3,5). Noise exposure during sleep causes sleep fragmentation and sleep periods that are too short thus leading to a situation of severe life stress known to initiate cerebral oxidative stress (for example, by increasing angiotensin II signalling and NOX2 activation), all of which can trigger inflammation of the brain microvasculature[128]. Animals exposed to noise also have increased circulating levels of angiotensin II[78,129]. The activation of the SNS in animals by NOX2-induced oxidative stress provides the link between RAAS-mediated NOX2 activation and a subsequent release of catecholamines[130,131]. In turn, catecholamines can initiate oxidative stress by promoting monoamine oxidase activity[132] or by activating astrocytes, microglia and NOX2 (REF.[133]). In accordance with the concept of a RAAS–ROS–SNS axis, treatment with a NOX inhibitor reduced blood pressure and angiotensin II and noradrenaline levels in hypertensive mice[134]. By contrast, blockade of the type 1 angiotensin II receptor and inhibition of angiotensin-converting enzyme decreased oxidative stress in the heart and the vasculature[135,136]. In mice, aircraft noise exposure (mean SPL 72 dB(A)

for 4 days) increased the expression of endothelin 1 in the aorta, a potent vasoconstrictor and activator of NOX2 activity[78,115,137], which is in part RAAS dependent[138].

In summary, these data provide molecular and pathophysiological evidence to explain the observed increase in endothelial dysfunction and hypertension in animal models in response to (aircraft) noise, with a central role of NOX2-triggered oxidative stress and inflammation as well as the impairment of circadian rhythm by sleep fragmentation and deprivation. The animal data strongly support the central role of stress-response pathways in the adverse cardiovascular and cerebral effects of noise in humans by providing detailed molecular mechanisms for the sequence of events in the brain and the stress-response axis. An in-depth discussion of the major limitations of animal models of noise exposure is provided in BOX 3.

Other emerging effects of noise exposure

Gut microbiota. Alterations to the gut microbiota can promote cardiometabolic diseases[139,140]. The gut microbiota–brain axis has been identified as a central mediator in the development of neuropsychiatric disorders



and intestinal inflammatory disease as well as in the regulation of mood and behaviour[141,142], all of which are linked to increased cardiovascular risk. Chronic noise exposure (SPL 88–98 dB(A) (control group SPL <40 dB(A)), 4 h per day during the sleep phase for 30 days) resulted in alterations to the gut microbiota–brain axis in a mouse model of Alzheimer disease[143]. In these mice, chronic noise exposure was associated with cognitive impairment, amyloid-β accumulation, decreased neurotransmitter levels, increased markers of neuroinflammation, and impaired intestinal and brain endothelial tight junction protein expression. Analyses of 16S ribosomal RNA (rRNA) sequencing data revealed changes in the flora of intestinal bacteria.

A proof-of-concept for a role of the gut microbiota–brain axis was established by transplantation of faeces from noise-exposed mice (SPL 98 dB(A)) to unexposed mice demonstrating that the recipient mice also developed an Alzheimer-like phenotype[143]. Alterations to the gut microbiota were also reported in chronically noise-exposed rats with the use of a similar exposure protocol[144]. Noise exposure also induced metabolic changes and increased levels of inflammatory cytokines (TNF and IL-1β), which were associated with an increase in health-compromising proteobacteria and a decrease in health-promoting actinobacteria (as measured by 16S rRNA sequencing)[144]. In another study, changes to the gut microbiota in rats after exposure to construction noise were associated with alterations in body weight and haematological parameters as well as with histopathological changes in the organs[145]. A noise-triggered signalling pathway along the gut microbiota–brain axis was associated with an impairment of cognitive function, anxiety-like behaviour and higher serum corticosterone concentrations in rats, which were improved by probiotic treatment[146]. In summary, noise exposure might modulate the gut microbiota, with potential effects on the development of CVD[147].

Circadian rhythm. The disruption of the circadian rhythm is a known risk factor for CVD[148]. Studies have suggested that a high exposure to noise affects the circadian rhythm. The exposure of mice to continuous aircraft noise (mean SPL 72 dB(A)) for 4 days) caused changes to the expression pattern of circadian genes in the aorta and kidneys[115]. The downregulation of *Foxo3* expression was one of the main changes in the aorta, which seemed to function as a central signalling hub regulating the circadian genes in the vascular tissue. Treatment with a FOXO3 activator ameliorated the noise-induced vascular oxidative stress and endothelial dysfunction in mice[115]. In addition, noise exposure downregulated the expression of *Per1* and upregulated the expression of *Arntl* (also known as *Bmal1*) and *Cry1* in the aorta. Other genes involved in the regulation of circadian rhythm were downregulated (*Nr1d1*, *Nr1d2* and *Rora*) or upregulated (*Cul1*, *Parp1*, *Prkag1* and *Prkag2*) by noise exposure. Additional studies revealed that daytime or night-time noise exposure induce distinct alterations in the RNA profile of clock genes in neurons of the inferior colliculus, an auditory structure essential for sound processing[149]. Of note, a central role for oxidative stress in the regulation of the circadian rhythm was previously established and termed 'redox control of cellular timekeeping'[150], and the contribution of environmental stressors was described[151]. Direct redox modifications in CRY, PER and FBXL3 (via thiol oxidation or reduction and zinc-sulfur complex formation or disruption) regulate the binding of PER and FBXL3 to the CLOCK–BMAL1 complex, leading to its inhibition[152]. In addition to this direct redox regulation, the clock system is regulated by the ROS-dependent and nitrogen species-dependent activation of redox-sensitive kinases, histone deacetylases, stress response proteins and transcription factors, all of which are modulated by environmental stressors[151].

◀ Fig. 5 | **Adverse health effects of aircraft noise exposure in mice.** In the brain, aircraft noise exposure causes sleep disturbance and stress responses via the activation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS), which leads to increased release of stress hormones, neuronal activation and secondary activation of the renin–angiotensin–aldosterone system (RAAS) and endothelin 1 (ET1) upregulation. Noise exposure also induces neuroinflammation and cerebral oxidative stress via the activation of NADPH oxidase 2 (NOX2) and uncoupling of neuronal nitric oxide synthase (nNOS). NOX2 activation is mediated by type 1 angiotensin II (Ang-II) receptor–diacylglycerol (DAG)-dependent protein kinase C (PKC) stimulation, as demonstrated by the presence in the brain of the pMARCKS marker, the phosphorylation of $p47^{phox}$ at serine 328, inflammation and oxidation markers, decreased nNOS levels and the downregulation of genes related to antioxidant responses (such as genes encoding catalase and forkhead box protein O3 (FOXO3)). nNOS uncoupling was demonstrated by the presence of phosphorylation at serine 847 (mediated by reactive oxygen species (ROS)-dependent activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII)) and the partial suppression of ROS formation by treatment with a selective nNOS inhibitor. The released stress hormones have direct vasoconstrictor effects on the systemic vasculature and adversely affect the heart, lungs and immune cells. In lung endothelial cells, noise exposure upregulates the expression of *Nox1*, *Nos3* (which encodes endothelial NOS (eNOS)) and genes related to the antioxidant defence, suggesting a counter-regulatory mechanism against pulmonary oxidative stress. In the heart, noise exposure upregulates markers of oxidative stress and eNOS and NOX2 activity and downregulates FOXO3 and connexin 43, all of which reflect cardiac remodelling and fibrosis. In the aorta, sleep disturbance induced by aircraft noise dysregulates genes related to the circadian clock, vascular signalling and remodelling, cell death and antioxidant defence. Noise exposure increases immune cell infiltration of the aorta and the levels of inflammation markers, including inducible NOS (iNOS). eNOS levels increase but nitric oxide (NO) bioavailability decreases. High NOX2 activity leads to increased formation of superoxide (O_2^-) that reacts with NO, generating the highly reactive peroxynitrite ($ONOO^-$), which causes protein damage and eNOS uncoupling by oxidizing the eNOS cofactor tetrahydrobiopterin (BH_4), leading to decreased NO bioavailability. eNOS uncoupling after noise exposure has also been demonstrated by the increased S-glutathionylation (GSS) of the enzyme and by the reduction of vascular superoxide production with the use of the NOS inhibitor L-NAME. Noise exposure increases the levels of circulating markers of oxidative stress and inflammation but decreases the levels of the antioxidant glutathione (GSH). Circulating leukocytes from noise-exposed animals show signs of oxidative DNA damage (8-oxo-2'-deoxyguanine (8-OH-dG)) and a compensatory increase in glutathione peroxidase 1 (GPX1) levels as well as a pronounced oxidative burst. Mitochondria of noise-exposed animals show increased swelling, cristolysis and DNA damage, impaired mitochondrial permeability transition pore (MPTP) function and Ca^{2+} handling, and monoamine oxidase (MAO) activation induced by high noradrenaline (NA) levels. The increased oxidative stress and inflammation in different tissues and fluids promotes the development of cardiometabolic diseases and cognitive impairment. The pharmacological activation of FOXO3 and deletion of *Nox2* largely prevent aircraft noise-induced adverse health effects in mice. The scheme is based on data from REF.[122]. 3-NT, 3-nitrotyrosine; 8-isoP, 8-isoprostane; ACTH, adrenocorticotropic hormone; BH_2, bihydrobiopterin; CCL2, CC-chemokine ligand 2; CRH, corticotropin-releasing hormone; DHFR, dihydrofolate reductase; GCH1, GTP cyclohydrolase 1; GFAP, glial fibrillary acid protein; H_2O_2, hydrogen peroxide; hsCRP, high-sensitivity C-reactive protein; MDA, malondialdehyde; P, phosphate group; pVASP, phosphorylated vasodilator-stimulated phosphoprotein; PYK2, protein-tyrosine kinase 2; VCAM1, vascular cell adhesion protein 1.

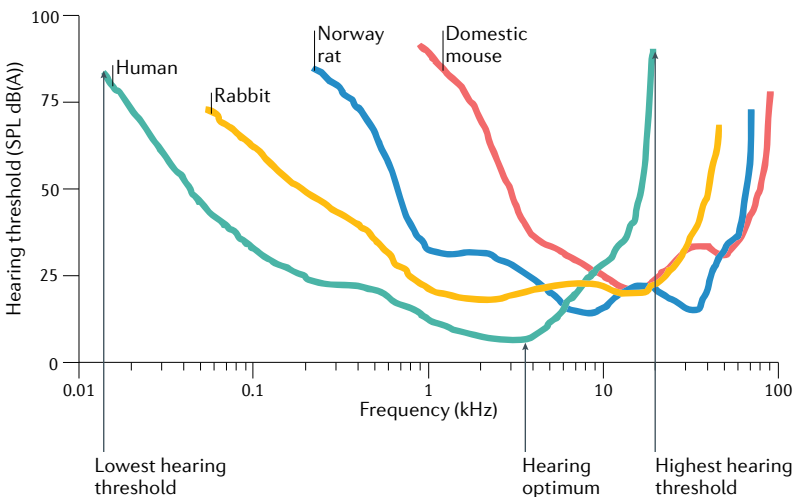
Epigenetic regulation. Epigenetic factors contribute to CVD via the modulation of atherosclerosis[153,154]. In addition to regulating coding RNA, noise-induced vascular and mental stress are known to cause changes in the expression patterns of non-coding RNA, especially of health-relevant microRNAs[155]. Noise-induced changes in microRNAs can occur through the indirect pathway, mainly mediated by stress-response pathways. The upregulation of miR-134 and miR-183 in the central amygdala in response to acute stress seems to be important[156] because both microRNAs are upregulated in patients with CAD and depression. DNA methylation is a central epigenetic pathway and an important form of transcriptional regulation affecting cardiovascular health and disease[157]. Changes in the DNA methylome (the total status of DNA methylation that determines its transcriptional activity) were demonstrated in the brains of noise-exposed rats (mean SPL 70–75 dB(A) with 20–4,000 Hz during the night for 3 days or 3 weeks), suggesting the epigenetic regulation of metabolism, especially in response to stress hormones[158].

Box 3 | **Limitations of animal studies on noise exposure**

The main limitation of animal studies is the different hearing range between species (see the figure). Whereas humans hear low-frequency noise (almost down to 0.01 kHz), the lower hearing threshold of mice is at 1 kHz. The hearing optimum for mice is at almost tenfold higher frequencies than for humans. The human upper hearing threshold is at 16–18 kHz, whereas that of mice is at almost 100 kHz. These differences in hearing thresholds and optimum influence the perception of noise and create differences between humans and animal models that might pose problems for the translation of results in animal models to the human setting. Therefore, multidisciplinary research approaches are of great importance such as by combining cardiovascular research with behavioural or sleep research. The determination of neuronal and psychological parameters might allow a better characterization of the perception of noise, even in animals. However, an inherent limitation of animal noise research is that 'perception' in animals cannot be accurately estimated because one cannot easily define when an animal is 'annoyed', which is an important factor for the daytime noise exposure health effects in humans. Annoyance might be an important determinant for the daytime noise neuropsychological effects, and some individuals might be more resilient to noise-induced annoyance than others.

Another problem of previous animal research might be the use of a high mean sound pressure level (SPL) of >85 dB(A) (often exceeding 100 dB(A)), whereas significant health effects in humans are typically observed at ≥55 dB(A) average SPLs. The general population is typically exposed to average SPLs of 45–65 dB(A), whereas 85 dB(A) is equivalent to a continuous exposure to the SPL of a ringing telephone or passing truck and 100 dB(A) is equal to the SPL of a jackhammer (see the dB(A) scale in FIG. 2a). Chronic exposure to 85 dB(A) can cause hearing loss in humans and exposure to ≥100 dB(A) can even cause acute damage to the inner ear. Accordingly, animal studies applying a mean SPL of ≥85 dB(A) might be hard to translate to the cardiovascular, metabolic and neuropsychological noise effects in humans and instead represent models to study chronic and acute hearing loss due to damage to inner ear structures. For these reasons, our group established a noise-exposure model for mice with the use of aircraft noise patterns of multiple take-off and landing events[78,115,120,121]. These aircraft noise patterns comprised all frequencies between 0.03 kHz and 20 kHz, contained irregular breaks and crescendo–decongestant phases to prevent early adaptation, and were played back with an average SPL of 72 dB(A) and peak sound levels of 85 dB(A), almost recreating the exposure characteristics in the daily life of individuals living near airports. An important argument for the validity of our chosen mouse model might be that we find striking similarities between the adverse effects of aircraft noise on the cardiovascular system in mice and those in humans (as shown in field studies) because night-time aircraft noise causes an increase in blood pressure and stress hormones levels as well as endothelial dysfunction and increased oxidative stress in the vasculature.

Curves are based on audiograms from previous studies in domestic mice[177], Norway rats[178], rabbits[179] and humans[180,181].



Multi-exposure perspective for noise

To study the health consequences of the environment, a new paradigm has been developed: the exposome, defined as the lifelong sum of all the environmental contributions to human physiology and pathophysiology[13] (BOX 1). In addition to external environmental stressors (such as transportation noise and air pollution), lifestyle and more general environmental factors (such as socioeconomic status and climate) also define the individual exposome[159]. At present, no studies have addressed transportation noise as part of the exposome with an attempt to disentangle the complexity of the various external and internal environmental factors. However, studies performed in 2018–2019 adjust for other external pollutants, mainly air pollution, and for a number of lifestyle exposures such as smoking and alcohol intake[31,32,160]. Furthermore, a few studies have investigated the interactions between noise and air pollution and lifestyle factors, such as smoking[160,161], or have studied the mutual effects of traffic noise and air pollution owing to their interconnected nature[42,96,98,162,163] (FIG. 1). However, more studies are needed before conclusions can be made (BOX 1).

The exposure to most environmental stressors activates a specific set of pathophysiological pathways comprising stress hormone signalling, oxidative stress and inflammation[72,151,164]. As a consequence, ongoing and future exposome studies will face a major challenge in identifying the differences in biochemical signatures (specific footprints) of different environmental stressors[165]. In addition, oxidative stress and inflammation also have a major role in the pathophysiology of cardiovascular, neurodegenerative and metabolic diseases, which makes the aims of exposome research even more ambitious. Given that environmental stressors, unhealthy lifestyles and classic risk factors activate the same central pathophysiological mechanisms as environmental stressors, additive and synergistic effects must be expected, leading to the exacerbated aggravation of non-communicable diseases[166,167]. Environmental stressors such as noise, air pollution and psychosocial stress accumulate in big cities and large urbanized areas, with the consequence that their combination induces health problems and increases a disease burden that exceeds even the most pessimistic approximations.

Noise-mitigation strategies

Different strategies to abate levels of road, rail and aircraft noise can be applied by the local authorities. For road traffic, noise generated by the contact between the tyres and the road surface is the dominating sound at speed levels >30–35 km/h for cars and >55–65 km/h for heavy vehicles. Therefore, replacing combustion engine cars with battery-driven electric cars will result in only minor reductions in road traffic noise (approximately 1 dB(A) reduction). Generally applied strategies to reduce road traffic noise are the building of noise barriers along busy roads in densely populated areas (up to 10 dB(A) reduction), the paving of road and highways with noise-reducing asphalt (3–6 dB(A) reduction) and reducing speed limits (10 km/h approximately 1 dB(A) reduction; 20 km/h approximately 2 dB(A) reduction). Furthermore, developing and promoting low-noise tyres have the potential to reduce noise levels at a national scale by 2–3 dB(A). Given that many of these abatement strategies result in fairly small reductions in noise, a combination of strategies might be relevant in highly exposed urban settings.

For aircraft noise, generally applied strategies to reduce exposure of the general population include the planning of air traffic routes to minimize overlap with densely populated areas, night-flight bans in which take-off and landing are not allowed, and the implementation of new continuous descent procedures such as a steeper descent with lower, less variable throttle settings. For railway noise, grinding of the railway tracts, replacing cast-iron block breaks with composite materials and the implementation of night bans are among the preferred strategies for reducing noise. Lastly, people living in noise-polluted houses or apartments can reduce indoor noise levels through the installation of sound-reducing windows.

Conclusions

The preclinical, clinical and epidemiological evidence summarized in this Review supports the concept that transportation noise might be an important environmental cardiovascular and cerebrovascular risk factor that contributes to the development of chronic CAD, acute coronary syndrome, arterial hypertension, stroke, mental disease, arrhythmia, heart failure and cardiometabolic disease. The results of translational animal and human studies provide strong evidence that noise is closely associated with an impairment of redox balance and vascular function in the brain and cardiovascular system and with the dysregulation of autonomic and metabolic processes. These alterations not only potentiate the adverse effects of traditional cardiovascular risk factors (such as arterial hypertension and diabetes) but also accelerate atherosclerotic processes and increase cardiovascular risk. However, we should emphasize that noise research conducted on animals cannot always be fully translated to the effects of noise on human health because species-specific differences in the hearing range and noise perception might yield varying results in different species that should be interpreted with caution (BOX 3).

Noise and air pollution have many of the same sources such as aircraft, railways and road vehicles. A report by the European Commission estimates a cost of €1 trillion per year from premature death and disease caused by environmental pollution, which far exceeds the costs caused by alcohol consumption and smoking[168]. Therefore, research gaps that need to be addressed are numerous and include the magnitude and time course of response to the co-exposure of noise and air pollution, the synergistic effects of both exposures on surrogate measures (such as blood pressure and diabetes mellitus), the duration of effect and time course of reversal, the influence of cardiovascular therapy on the effects by noise and air pollution on future cardiovascular risk, the effect of noise on the circadian rhythm, and the combined effects of noise and lifestyle factors (such as diet, stress and exercise). We also need to address whether CVD drugs that improve prognosis in patients with CVD and cerebrovascular disease, such as angiotensin-converting enzyme inhibitors, type 1 angiotensin II receptor blockers or statins, reduce the noise-induced adverse health effects. What should be the political consequences of the adverse effects of noise? The cardiovascular community has a responsibility to help to promulgate the health effects of environmental factors, not only via the promotion of healthy lifestyles but also by minimizing the effect of noise pollution on cardiovascular health. Importantly, noise pollution was mentioned for the first time in the 2020 ESC guidelines for chronic coronary syndromes[169], but recommendations to reduce noise pollution were missing in the 2016 ESC guidelines for the prevention of CVD[5,170].

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Review criteria
For the mechanistic discussion of human data, we have mainly considered translational human studies from the past 20 years with a focus on the cardiovascular system or on stress, inflammatory and oxidative pathways related to cardiovascular disease. Experimental research on the cardiovascular or neuropsychological effects of transportation noise in humans is scarce. For the discussion on animal models, we focus on studies from the past 20 years that did not relate only to hearing loss. Research on the cardiovascular effects of non-auditory noise in animals is very rare. For the period before 2000, we selected only the landmark studies.

Supplementary information
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