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HURT BY NOISE

Sound from cars, aircraft, trains, and other man-made machines is more than just annoying. It increases the risk of cardiovascular disease.

BY THOMAS MÜNZEL AND OMAR HAHAD

More than 100 years ago, the German physician and Nobel Prize winner Robert Koch predicted that "one day mankind will have to fight the burden of noise as fiercely as plague and cholera." He was right. While many sounds in our environments are quite pleasant, noise, defined as unwanted sound, has the potential to cause real damage to our bodies and minds.

The principal sources of environmental noise are transportation and industrial operations. Since Koch's time, researchers have come to recognize that such noise can cause sleep disturbances, elicit anger, and trigger conditions such as tinnitus and coronary heart disease caused by reduced blood flow to the organ. Noise can also lead to memory and learning impairments in children. In 2011, the World Health Organization (WHO) concluded that exposure to transportation-related noise—specifically from aircraft, vehicles, and trains—is responsible for the annual loss of up to 1.6 million cumulative years of healthy life among people in Western Europe. [1]

The cardiovascular burden of traffic noise is particularly insidious, with annoyance reactions and sleep disturbances leading to an increased risk of heart disease. A 2015 report from the European Environment Agency linked exposure to car, truck, plane, and train sounds with nearly 1.7 million additional cases of hypertension, 80,000 additional hospital admissions, and 18,000 premature deaths due to coronary heart disease and stroke in Europe each year.[2] A few years later, a metaanalysis conducted on behalf of the WHO supported these conclusions, with seven high-quality longitudinal studies collectively establishing that road traffic noise exposure was associated with an 8 percent increased risk of coronary heart disease.[3]

In addition to being associated with an increased incidence of coronary heart disease, noise may serve as an acute trigger of cardiovascular problems. For example, a study published earlier this year established that for nighttime deaths, noise exposure levels two hours preceding death were significantly associated with heart-related mortality.[4]

Despite these indications of the hazards of noise, research concerning adverse health effects of noise pollution is not well supported financially or politically, and the underlying mechanisms by which noise increases the risk of cardiovascular disease are not well understood. Our research group in the Department of Cardiology at the University Medical Center of the Johannes Gutenberg University of Mainz in Germany and others aim to uncover these pathophysiological processes. This will not only provide a method for quantifying the degree of physiological stress triggered by noise, but also help to identify novel pharmacological agents or noise mitigation measures that could be used to prevent, manage, or treat noise-induced disease.

Indirect harm

In 1950, Karl Kryter, then the director of the Operational Applications Laboratory at the Air Force's Air Research and Development Command in Washington, DC, emphasized the potential health effects of the so-called nonauditory effects of noise.[5] He proposed that such effects are the result of the stimulation of the body's neural systems that are not exclusively linked to audition, including the autonomic nervous system, which controls systemic responses and arousal reactions of an organism, and the cortical and subcortical brain centers responsible for cognitive performance.

In 1968, Gerd Jansen from the Max Planck Institute of Molecular Physiology in Dortmund, Germany, provided evidence linking noise to cardiovascular problems. Examining 1,005 German industrial workers, Jansen reported the occurrence of physiological changes such as peripheral circulation issues, heart problems, and equilibrium disturbances, which were more pronounced in very noisy industries compared with less noisy industries.[6] These early observations hinted that chronic noise exposure may cause cardiovascular disease, but it was unclear how.

In 2003, Wolfgang Babisch, a senior research officer at the German Federal Environmental Agency, developed the noise reaction model, which describes two pathways for determining the adverse health effects induced by noise. In the first, known as the auditory/direct pathway, exposure to noise louder than 90–100 decibels (such as a jackhammer) causes inner-ear damage that can lead to hearing loss and tinnitus. In the second, the nonauditory or indirect pathway, low-level noise exposure of 50–60 decibels (such as a conversation) interferes with communication, concentration, daily activities, and sleep, resulting in annoyance, mental stress, and subsequent sympathetic and endocrine activation.[7] It was the latter pathway that Babisch suspected was the central player for noise-induced cardiovascular effects.

Specifically, he hypothesized that if the exposure is persistent and chronic, noise contributes to a pathophysiological phenotype that is characterized by increased stress hormone levels, high blood pressure, and accelerated heart rate. As a consequence, the body generates its own cardiovascular risk factors, including high cholesterol and glucose levels, increased blood viscosity, and activation of blood coagulation. If stress persists for years, cardiovascular diseases such as hypertension, coronary heart disease, heart failure, arrhythmia, and stroke can begin to manifest, along with mental stress or related disorders such as depression and anxiety, which are themselves known to negatively affect cardiovascular health.

Translational aircraft studies in people

In 2013, to take a more controlled look at the effects of traffic noise, we and our colleagues conducted our first field study involving the exposure of healthy subjects to simulated aircraft noise overnight in their homes. On control nights, we simply had participants play a recording of normal background noise in their home on a standard portable audio system placed on their nightstands. On other nights, we had them play a looped recording of aircraft noise taken in the bedroom of a resident living in the vicinity of Düsseldorf airport in Germany with a window tilted open.

Using questionnaires, blood analyses, and physiological tests of endothelial function, we established that one night of simulated aircraft noise exposure reduced self-reported sleep quality, elevated circulating levels of stress hormones such as adrenaline, stiffened blood vessels, and caused vascular endothelial dysfunction, the latter two reflecting early subclinical signs of atherosclerosis and being independent predictors of future cardiovascular events and disorders.[8] Importantly, comparing participants exposed to 30 versus 60 aircraft noise events per night revealed a dose-dependent worsening of endothelial function.[9] Moreover, previous exposure to 30 aircraft noise events caused 60 events to have larger adverse effects on endothelial function. Thus, rather than any sort of habituation to the noise, there appeared to be a priming effect: prior exposure amplified the negative effect of noise on endothelial function.

EXPOSURE TO TRANSPORTATION-RELATED NOISE IS RELATED TO THE ANNUAL LOSS OF UP TO 1.6 MILLION CUMULATIVE YEARS OF HEALTHY LIFE AMONG PEOPLE IN WESTERN EUROPE.

—World Health Organization, data from 2011

More recently, we exposed healthy subjects to simulated nighttime train noise and similarly found that one night of exposure greatly impaired sleep quality and endothelial function. In addition, proteomic analysis of participant blood samples revealed substantial changes in circulating proteins that pointed to a higher susceptibility to inflammation and blood clotting.

Only a few other studies have provided mechanistic insight into the relationship between traffic noise exposure and cardiovascular disease. In 2017, Maria Foraster and her colleagues at the Swiss Tropical and Public Health Institute found, much as we did, that a decade of exposure to nighttime noise events, mainly related to road traffic noise, was associated with increased arterial stiffness in a cohort of 2,775 Swiss participants.[10] That same year, a pooled analysis of more than 144,000 people in two large European cohorts from Norway and the Netherlands indicated that long-term exposure to road traffic noise was associated with higher levels of inflammation, blood lipids, and fasting glucose.[11]

Babisch proposed that annoyance reactions to noise may play an important role in the extent to which noise-exposed subjects develop cardiovascular disease.[12] That is, it's not the noise itself that's a problem, but one's emotional reaction to it. In 2019, Michael Osborne of Massachusetts General Hospital and colleagues demonstrated that, after five years of exposure to transportation noise such as that caused by road and aircraft traffic, higher activity in the amygdala, a brain region involved in emotional processing, stress perception, and emotional reactions, is linked with an increased risk of heart attack, stroke, heart failure, and death through mechanisms involving heightened arterial inflammation.[13] Noise annoyance, it seems, is a so-called effect modifier, meaning that the cardiovascular side effects of noise are greater in people who are getting annoyed and therefore experiencing increased stress responses compared with those who are not.

Whatever the cause, evidence is now accumulating to demonstrate that noise pollution is resulting in endothelial dysfunction, ultimately leading to high blood pressure, arrhythmia, heart attack, heart failure, and stroke.[14]

Molecular mechanisms

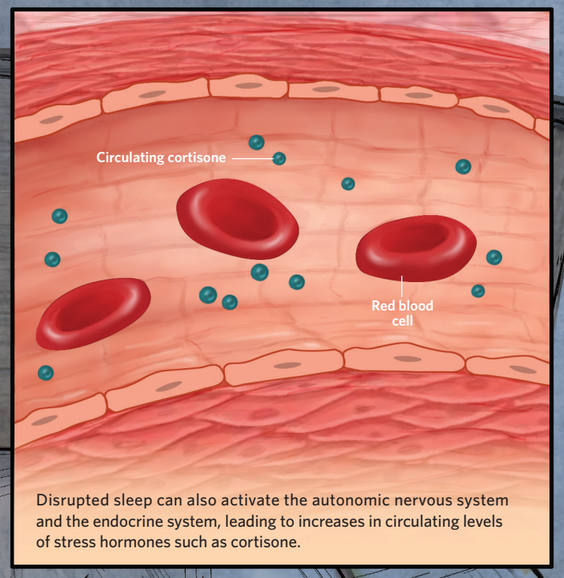
A surprising result to come out of our first field study was that the adverse effects of nighttime noise on endothelial function were ameliorated by the administration of vitamin C, which we gave to some participants after noise exposure. Vitamin C is an antioxidant, a scavenger of oxygen-derived free radicals. Thus, this finding hinted that increased oxidative stress within the vasculature may be responsible for noise-induced endothelial dysfunction.

Nighttime noise can disrupt sleep and cause cognitive and emotional responses via activation of the amygdala.

NOISE DAMAGE PATHWAYS

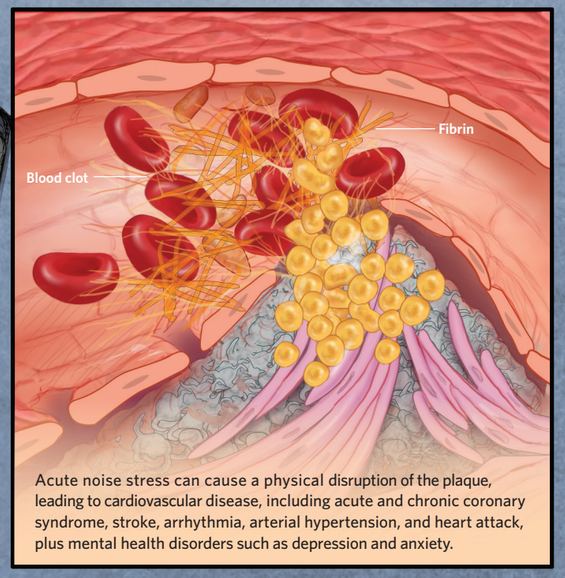
Epidemiological data have long linked exposure to noise such as aircraft, railway, or traffic sounds to increased risks of cardiovascular disease. And in recent years, experimental work has been revealing the biological mechanisms underlying that link. Specifically, researchers are finding that noise activates the brain's limbic system, which plays a role in emotional regulation, the release of stress hormones into the blood, and controlling of the sympathetic nervous system. These stress responses can lead to cerebral and vascular inflammation, oxidative stress, and altered gene expression, sometimes culminating in endothelial dysfunction and cardiovascular disease.

NOISE STRESS REACTIONS



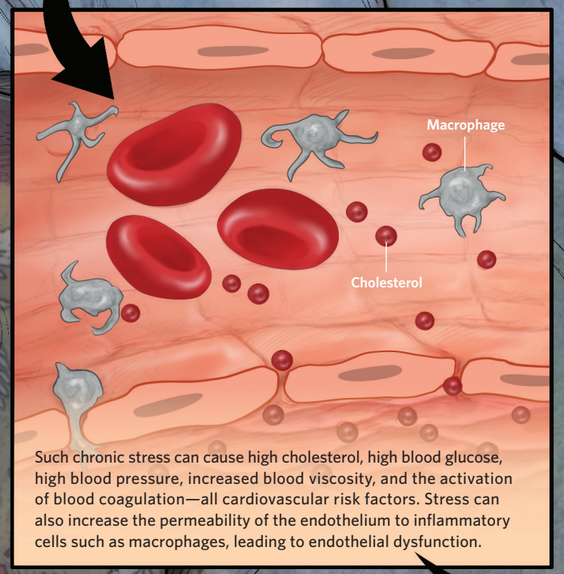
Disrupted sleep can also activate the autonomic nervous system and the endocrine system, leading to increases in circulating levels of stress hormones such as cortisone.

NOISE-TRIGGERED PLAQUE RUPTURE



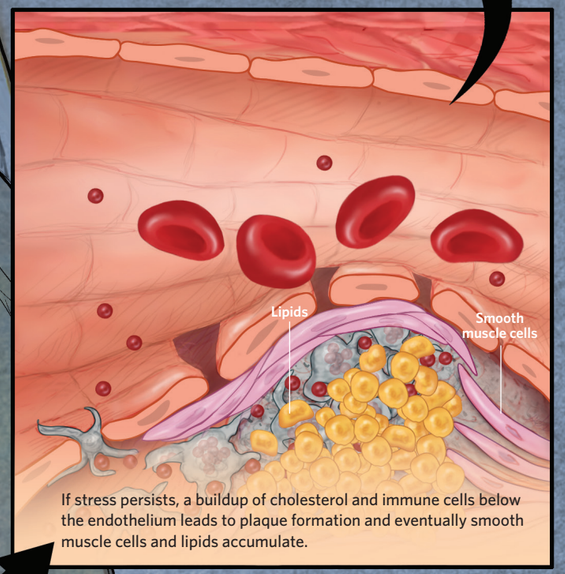
Acute noise stress can cause a physical disruption of the plaque, leading to cardiovascular disease, including acute and chronic coronary syndrome, stroke, arrhythmia, arterial hypertension, and heart attack, plus mental health disorders such as depression and anxiety.

ENDOTHELIAL DYSFUNCTION



Such chronic stress can cause high cholesterol, high blood glucose, high blood pressure, increased blood viscosity, and the activation of blood coagulation—all cardiovascular risk factors. Stress can also increase the permeability of the endothelium to inflammatory cells such as macrophages, leading to endothelial dysfunction.

PLAQUE BUILDUP



If stress persists, a buildup of cholesterol and immune cells below the endothelium leads to plaque formation and eventually smooth muscle cells and lipids accumulate.

UNLIKE OTHER MAJOR CARDIOVASCULAR RISK FACTORS, NOISE POLLUTION CANNOT BE TREATED BY DOCTORS AND PATIENTS BUT RATHER BY POLITICIANS.

To further elucidate the molecular mechanisms responsible for nonauditory noise-induced cardiovascular side effects, we established a novel mouse model and employed various noise pollution protocols. In the first study, we exposed mice to simulated aircraft noise around the clock for four days and observed increased blood pressure and elevated concentrations of stress hormones such as cortisol, noradrenaline, angiotensin II, and dopamine, along with raised blood pressure, suggesting the animals were stressed.[15] This was accompanied by endothelial dysfunction and increased production of reactive oxygen species (ROS) within the vascular wall.

Blood vessels are lined with endothelial cells that produce powerful vasoconstricting and vasodilating substances such as the radical nitric oxide ($NO^{\cdot}$). But ROS—which are produced in cases of hypertension, high cholesterol, diabetes, chronic smoking, and other conditions that are risk factors for cardiovascular disease—attack and degrade $NO^{\cdot}$, thus limiting its bioavailability. This leads to stiffer vessels, higher blood pressure, and the initiation of plaque buildup in arteries. It appeared that this might be the initial pathway by which noise causes cardiovascular damage.

In addition to the increased production of ROS in the vasculature, our mouse study revealed that noise could trigger oxidative stress in the brain. In a subsequent study, which followed the same noise exposure protocols as the first mouse study, we confirmed high ROS levels in the frontal brain region of mice and documented significant neuroinflammation in that area.[16] This observation is particularly interesting because these cerebral effects may explain, at least in part, the impaired cognitive development seen in children exposed to noise.

We identified two radical-forming enzymes, the phagocytic nicotinamide adenine dinucleotide phosphate oxidase isoform 2 (Nox2) and endothelial nitric oxide synthase (eNOS), as sources for increased ROS production in our noise-exposed mice. Nox2 is mainly found in inflammatory cells such as macrophages and monocytes, and the eNOS we detected tended not to be coupled with its cofactor or substrate. Under normal conditions, eNOS produces NO, which has important vasodilating and anti-atherosclerotic effects, but after noise, the enzyme becomes "uncoupled"—it switches to a pro-atherosclerotic state, producing the reactive oxygen species superoxide (O_2^{-}) instead of NO.

Indeed, mice lacking the Nox2 gene suffered almost no ill effects from noise exposure, confirming oxidative stress as a key player in noise-induced cerebral and cardiovascular damage. We also detected a downregulation of genes encoding antioxidant pathways as well as evidence for more inflammation of the vasculature, which may further increase oxidative stress and thus may aggravate endothelial dysfunction and arterial hypertension.

Importantly, we did not observe these outcomes in a control group of mice, which was exposed to white noise at the same volume as the animals in the aircraft-exposure group. This indicates that the sound pressure level per se is not causing the damage. Moreover, the effects were only seen when the mice were exposed to noise during the day, when the animals are normally sleeping, suggesting that impaired sleep quality, including frequent fragmentation of sleep and/or too-short sleep, is a driver of noise-induced adverse health effects.

In all, the findings in humans and mice indicate that noise activates inflammatory and oxidative stress pathways in the vasculature and the brain, leading to endothelial and cerebral dysfunction. (See illustration on page 30.) This aligns with the pathophysiological pathways at play in traditional cardiovascular risk factors such as smoking, obesity, diabetes mellitus, and hypertension. These and the novel risk factor of noise appear to work similarly to increase cardiovascular risk.

Planning for a less noisy future

While the mechanisms underlying the cardiovascular side effects of environmental noise remain an active area of investigation, experimental and epidemiological studies from the last several years clearly demonstrate that exposure increases the risk of disease. Unlike other major cardiovascular risk factors, however, noise pollution cannot be treated by doctors and patients but rather by politicians.

Policies should work to bring noise exposure levels in line with the new guidelines developed by the WHO,[17] which lowered the recommendations for mean daily noise sound pressure levels to 45 decibels for aircraft noise, 53 decibels for road traffic noise, and 54 decibels for railway noise, with even stricter limits for nighttime hours, in order to reduce the burden of disease from noise.

Importantly, noise and air pollution have many of the same sources—aircraft, trains, and road vehicles. Research suggests that the direct and indirect social costs of noise and air pollution in the European Union could be nearly €1 trillion, accounting for premature death and disease. That far exceeds the costs caused by alcohol and smoking, which have been estimated to cost €50 billion– €120 billion and €540 billion, respectively. We must better understand the response to co-exposure to noise and air pollution, as well as the synergistic effects of both exposures on surrogate measures such as blood pressure and diabetes. Other open questions include the effects of cardiovascular therapy on noise- and air pollution–related cardiovascular risks and the influence of noise on circadian rhythms. Finally, we will need to address the combined effects of noise and lifestyle factors such as diet, stress, and exercise to fully tackle the noise problem. ■

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References

1. World Health Organization, "Burden of disease from environmental noise: Quantification of healthy life years lost in Europe," 2011.
2. Danny Houthuijs et al., "Health impact assessment for noise in Europe," ETC/ACM Technical Paper 2014/9 (Bilthoven, The Netherlands: European Topic Centre on Air Pollution and Climate Change Mitigation, 2015).
3. E. Van Kempen et al., "WHO environmental noise guidelines for the European region: A systematic review on environmental noise and cardiovascular and metabolic effects: A summary," *Int J Environ Res Public Health*, 15:379, 2018.
4. A. Saucy et al., "Does night-time aircraft noise trigger mortality? A case-crossover study on 24 886 cardiovascular deaths," *Eur Heart J*, 42:835–43, 2021.
5. K.D. Kryter, "The effects of noise on man," *J Speech Hear Disord Monogr Suppl*, 1:1–95, 1950.
6. G. Jansen, "Effects of noise on health," *Ger Med Mon*, 13:446–48, 1968.
7. W. Babisch, "Stress hormones in the research on cardiovascular effects of noise," *Noise Health*, 5:1–11, 2003.
8. F.P. Schmidt et al., "Effect of nighttime aircraft noise exposure on endothelial function and stress hormone release in healthy adults," *Eur Heart J*, 34:3508–14a, 2013.
9. J. Herzog 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*, 114:46, 2019.
10. M. Foraster 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*, 125:097004, 2017.
11. Y. Cai 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*, 38:2290–96, 2017.
12. W. Babisch et al., "Noise annoyance—a modifier of the association between noise level and cardiovascular health?" *Sci Total Environ*, 452–53:50–57, 2013.
13. M.T. Osborne et al., "A neurobiological mechanism linking transportation noise to cardiovascular disease in humans," *Eur Heart J*, 41:772–82, 2020.
14. T. Münzel et al., "Adverse cardiovascular effects of traffic noise with a focus on nighttime noise and the new WHO noise guidelines," *Annu Rev Public Health*, 41:309–28, 2020.
15. T. Münzel et al., "Effects of noise on vascular function, oxidative stress, and inflammation: mechanistic insight from studies in mice," *Eur Heart J*, 38:2838–49, 2017.
16. S. Kröller-Schön 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*, 39:3528–39, 2018.
17. World Health Organization, "Environmental noise guidelines for the European Region," 2018.