

REVIEW TOPIC OF THE WEEK

Environmental Noise and the Cardiovascular System



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ABSTRACT

Noise has been found associated with annoyance, stress, sleep disturbance, and impaired cognitive performance. Furthermore, epidemiological studies have found that environmental noise is associated with an increased incidence of arterial hypertension, myocardial infarction, heart failure, and stroke. Observational and translational studies indicate that especially nighttime noise increases levels of stress hormones and vascular oxidative stress, which may lead to endothelial dysfunction and arterial hypertension. Novel experimental studies found aircraft noise to be associated with oxidative stress-induced vascular damage, mediated by activation of the NADPH oxidase, uncoupling of endothelial nitric oxide synthase, and vascular infiltration with inflammatory cells. Transcriptome analysis of aortic tissues from animals exposed to aircraft noise revealed changes in the expression of genes responsible for the regulation of vascular function, vascular remodeling, and cell death. This review focuses on the mechanisms and the epidemiology of noise-induced cardiovascular diseases and provides novel insight into the mechanisms underlying noise-induced vascular damage. (J Am Coll Cardiol 2018;71:688-97) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

The global burden of disease has shifted within the last decades from communicable, maternal, perinatal, and nutritional causes to noncommunicable diseases, such as atherosclerosis (1). Although medical and scientific efforts have focused primarily on diagnosis, treatment, and prevention of traditional cardiovascular risk factors (e.g., diabetes, smoking, arterial hypertension, and hyperlipidemia) (1), recent studies indicate that also risk factors in the physical environment may facilitate the development of cardiovascular disease (CVD) (1). With industrialization and globalization, the importance of new environmental factors, such as noise and air pollution, is becoming increasingly evident. Within the last decade, several studies have found traffic noise (road, aircraft, and railway noise) to be

associated with increased risk of cardiovascular and metabolic diseases (2-4). Already in 2011, Babisch (4) published the statement “The question at present is no longer whether noise causes cardiovascular effects, it is rather: what is the magnitude of the effect in terms of the exposure-response relationship (slope) and the onset or possible threshold (intercept) of the increase in risk.” Until recently, the precise mechanisms underlying noise-induced CVD were largely unknown, mainly because of lack of models for translational research in humans and animals. Noise annoyance and chronic stress, activation of the autonomic and endocrine system, and disturbance of sleep are proposed to ultimately lead to pathophysiologic (vascular) alterations in the intermediate or chronic timeframe contributing directly



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or indirectly to initiation and progression of CVD (4,5). The present review focuses on novel translational noise studies, demonstrating which underlying molecular mechanisms may lead to impaired vascular function, and recent epidemiologic evidence of noise-induced CVD. We also address the nonauditory effects of noise and their impact on the cardiovascular system.

ADVERSE EFFECTS OF ENVIRONMENTAL NOISE ON THE AUTONOMIC NERVOUS SYSTEM AND CONSEQUENCES FOR THE CARDIOVASCULAR SYSTEM

According to the noise reaction model introduced by Babisch (5), CVD can be caused by an “indirect pathway,” where lower levels of noise disturb sleep, communication, and activities, with subsequent emotional and cognitive responses and annoyance. A resulting chronic stress reaction is proposed to ultimately lead to pathophysiologic alterations in the intermediate or chronic timeframe, which may result in manifest adverse health effects (5). Furthermore, chronic stress may also generate cardiovascular risk factors on its own, including increased blood pressure, glucose levels, blood viscosity and blood lipids, and activation of blood coagulation (5), which may ultimately lead to manifest CVD. Interestingly, emotional stress induced by nighttime aircraft noise exposure has been associated with stress cardiomyopathy (Takotsubo syndrome), a phenomenon that has been linked to excessive stress hormone release (6). Noise-induced annoyance has been proposed to act as an important effect modifier of the relationship between noise exposure and arterial hypertension (7) and ischemic coronary artery disease (8). In addition, high levels of environmental noise have been associated with mental health problems, such as depression and anxiety (9), conditions that are known to adversely affect cardiovascular function (10).

The molecular mechanisms behind the association between noise and vascular damage and CVD are not completely understood. It has been proposed that chronic stress reactions, by activation of the autonomic nervous system and increased levels of circulating cortisol (discussed previously) (4,5,11,12), may lead to vascular (endothelial) dysfunction, mainly through induction of oxidative stress (13,14) and subsequent activation of prothrombotic pathways and vascular inflammation (15). In addition to endothelial dysfunction, elevated blood pressure, dyslipidemia, changes in blood glucose levels, and altered heart rate variability could contribute to CVD development or progression. Importantly, these

pathophysiologic mechanisms are potentially not mutually exclusive, and may be active at different points in time following noise exposure, and vary in importance in relation to chronicity of exposure.

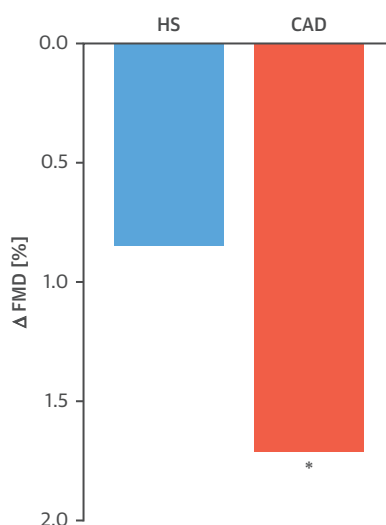
ADVERSE CARDIOVASCULAR EFFECTS OF NOISE IN HUMANS

Translational studies addressing associations between noise and vascular (endothelial) function are rare. In a recent field study, we found that simulated nocturnal aircraft noise was associated with endothelial dysfunction and decreased sleep quality (14). Importantly, endothelial dysfunction was markedly improved by acute administration of the antioxidant vitamin C, indicating that increased production of reactive oxygen species and/or depletion of antioxidant defense significantly contributes to this phenomenon. The associations between noise and endothelial function were found substantially more pronounced if the subject had been previously exposed to noise (priming effect). This indicates that the vasculature is rather sensitized than desensitized to vascular damage in response to repeated noise

ABBREVIATIONS AND ACRONYMS

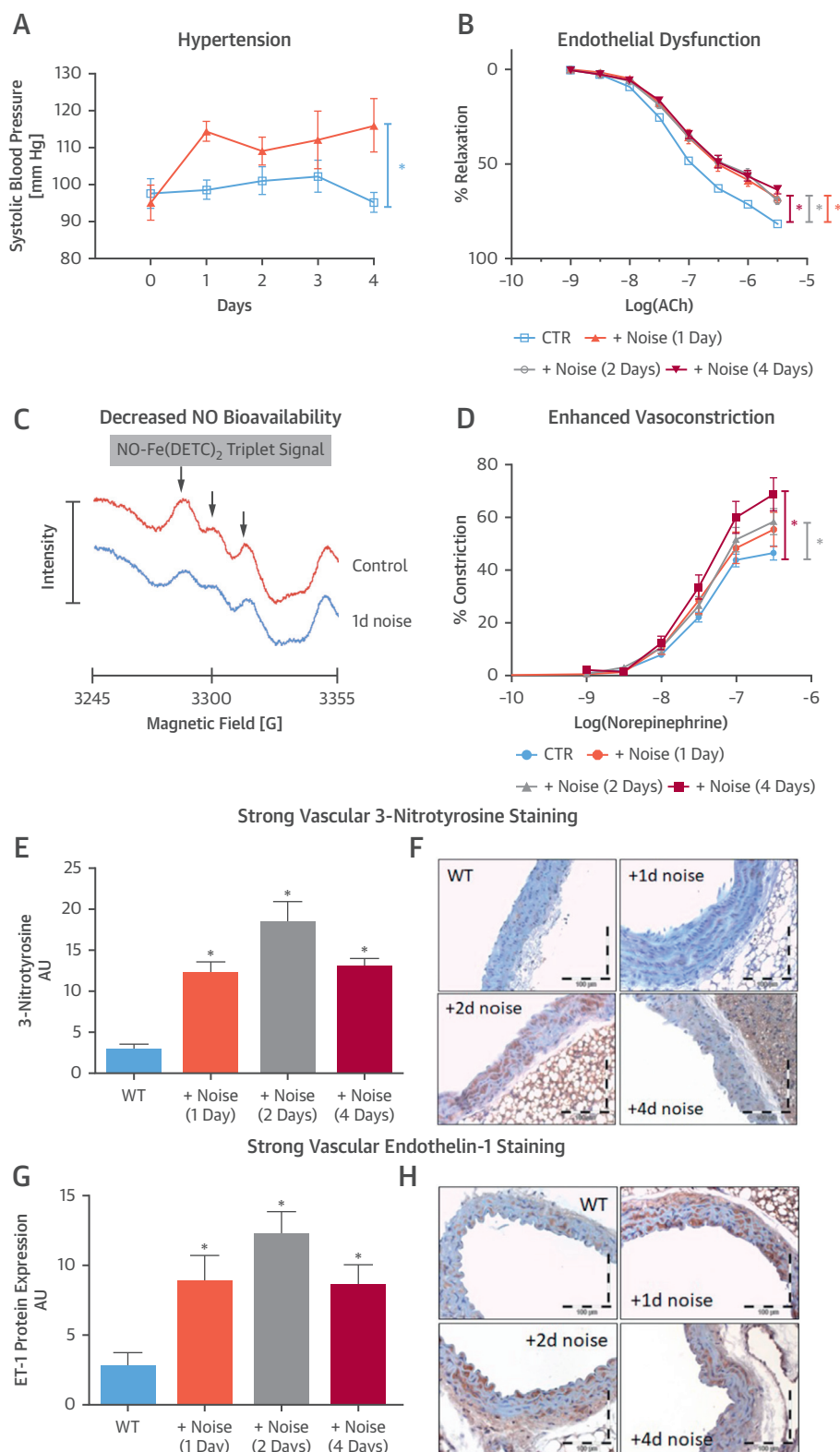
CVD = cardiovascular disease
eNOS = endothelial nitric oxide synthase

FIGURE 1 Impact of Aircraft Noise Exposure on Endothelial Function of Healthy Subjects and Patients With Established Coronary Artery Disease



Delta in flow-mediated dilation of the brachial artery in response to 60 nighttime aircraft noise events in healthy subjects (n = 70) (14) compared with patients with established coronary artery disease (n = 60) (13). *p < 0.05 versus HS group. CAD = coronary artery disease; FMD = flow-mediated dilation; HS = healthy subjects.

FIGURE 2 Adverse Cardiovascular Effects of Aircraft Noise Exposure in Mice



Continued on the next page

exposures. Noise-induced vascular dysfunction was found paralleled by increased levels of adrenaline. Furthermore, the negative association between noise and endothelial function was more pronounced in patients with established coronary artery disease (Figure 1) (13). Importantly, no correlation was observed between noise sensitivity or annoyance, suggesting that endothelial function deteriorates in response to nighttime noise, independently of whether there is an annoyance reaction or not (13). The study also found that simulated nighttime aircraft noise was associated with an increase in blood pressure. Thus, our observational studies may explain at least in part the results of the HYENA (Hypertension and Exposure to Noise Near Airports) study, which found a statistically significant association between nighttime aircraft noise and blood pressure (16). Associations between road traffic noise and CVD were found stronger among people sleeping with open windows or with bedroom facing the road (17). Nighttime noise may interfere with blood pressure dipping and thereby increase cardiovascular risk (18). Endothelial dysfunction was also observed in people working 24-h shifts (19) and in people exposed to chronic sleep restriction (20), suggesting that nighttime noise-induced sleep deprivation and fragmentation may be an important branch on the mechanistic pathway between noise exposure and endothelial dysfunction and CVD (21,22).

Importantly, endothelial dysfunction has been demonstrated to have prognostic value in patients with peripheral artery disease, arterial hypertension, acute coronary syndrome, or chronic stable coronary artery disease (23). Thus, noise-induced endothelial dysfunction may partly explain the association between transportation noise and CVD found in various epidemiological studies (24,25).

ADVERSE CARDIOVASCULAR EFFECTS OF NOISE IN ANIMALS

Noise in animal housing facilities is a major problem in animal studies, because it impacts hearing, behavior, and physiology in mice (26). The challenge

with this known confounder of animal studies becomes even more complex by variations in noise susceptibility of different animal species, strains, and their hearing frequencies. Nevertheless, effects of noise on animal (e.g., mice) blood pressure, vascular function, stress hormones, immune reactions, wound healing, body weight, fertility, and reproduction are well documented (27). Mechanistic studies in animals, however, addressing associations between noise exposure and vascular (endothelial) function and cardiovascular risk are rare. Noise exposure of monkeys (85 dB[A]), intermittent for 9 months) had no effects on the auditory system, but significantly increased blood pressure by 30 mm Hg (28). Other studies established that white noise exposure of rats for periods of 2 to 8 weeks (85 to 100 dB[A]) significantly impaired endothelium-dependent vasodilation (measured by acetylcholine in thoracic aorta or mesenteric arterial rings), increased the sensitivity to the vasoconstrictor serotonin, decreased the lumen sizes of microvessels, increased systolic blood pressure by 25 to 37 mm Hg and increased circulating markers of oxidative stress (29-32).

White noise exposure in the range of 70 to 100 dB(A) has been associated with increased levels of stress hormone, lipid peroxidation, and morphological changes in the heart of rats (33), and structural changes of the vasculature that were corrected by the antioxidant vitamin E (34). Chronic white noise exposure (100 dB[A]) also induced an intestinal inflammatory response in rats, with a persistent elevation of IgA, interleukin-1 β , and tumor necrosis factor- α levels. Thus, chronic noise exposure may directly or indirectly regulate gut microbiota-host inflammation homeostasis (35).

We recently developed an animal model for exposure of mice to aircraft noise events, with a maximum sound pressure level of 83 dB(A) and a mean sound pressure level of 72 dB(A). Our aim was to study the nonauditory effects of noise on the cardiovascular system, inflammation, and oxidative stress (24). Effects of continuous (24 h) aircraft noise exposure for 1, 2, and 4 days were compared with “white noise” as a control noise exposure, using exactly the same

FIGURE 2 Continued

Noise increases systolic blood pressure (A, orange), impairs endothelial function (B), reduces vascular nitric oxide levels (measured by electron paramagnetic resonance spectroscopy) (arrows indicate nitrosyl-iron triplet signal) (C), and enhances sensitivity to vasoconstrictors (D). (E and F) Noise causes substantial vascular 3-nitrotyrosine staining. (G and H) Noise increases vascular autocrine endothelin-1 production. Stainings reflect representative immunohistochemistry images. Brown color indicates nitrotyrosine or endothelin-1 staining. * $p < 0.05$ versus group without noise (CTR or WT). Adapted from Münzel et al. (24) with permission of the publisher. Copyright © 2017, Oxford University Press. CTR = control; ET-1 = endothelin-1; NO = nitric oxide; WT = wild-type.

average sound pressure level as for aircraft noise. The key findings were that aircraft noise was associated with increased blood pressure, endothelial dysfunction, reduced vascular nitric oxide formation, increased oxidative stress marker, and increased sensitivity of the vasculature to vasoconstrictors (**Figure 2**). Importantly, these changes were unique for aircraft noise and not observed in response to white noise exposure (applied in the form of a continuous swoosh) (24), suggesting that the characteristics of the noise stimulus (pattern, frequency, exposure time, and intensity) are important. Next-generation sequencing analysis showed that aortic tissues from aircraft noise-treated animals displayed significant changes of genes partly responsible for the regulation of vascular function, vascular remodeling, and cell death (24). A summary of the main mechanistic pathways including gene regulatory networks is provided at the end of this review and displayed in the **Central Illustration**.

EPIDEMIOLOGICAL EVIDENCE ON NOISE AND CVD

The quantity of epidemiological papers on traffic noise and CVD is rapidly growing, especially in recent years. At the same time, the research quality has increased considerably, with much larger study populations and increased focus on adjustment for air pollution. This has resulted in further evidence of traffic noise as a risk factor for major cardiovascular outcomes, such as coronary heart disease (25,36), and indicated that traffic noise may also be associated with major CVD not investigated previously in a noise context (37,38).

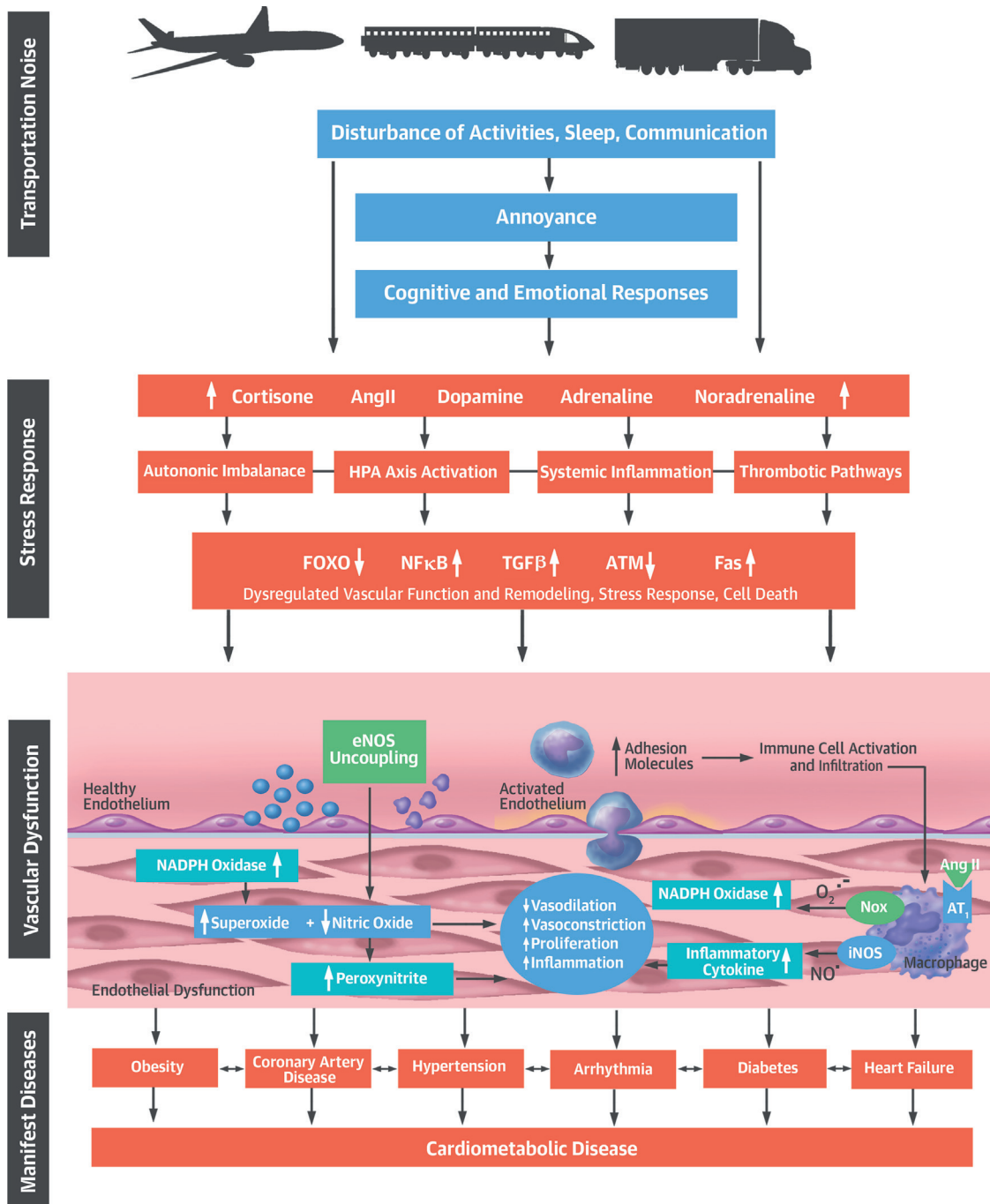
NOISE AND CVD. Since publishing of the first study in the late 1980s, the association between traffic noise and coronary heart disease has been studied extensively. Recent meta-analyses consistently conclude that traffic noise is associated with increased risk of coronary heart disease (25,36). The most recent meta-analysis from 2015 included studies on road traffic and aircraft noise, and found a 6% significant increase in risk for every 10 dB(A) increase in traffic noise (day-evening-night equivalent noise level A-weighted), starting as low as 50 dB(A) (25). Importantly, the meta-analysis applied strict quality criteria with regard to design, including only incident studies. The meta-analysis also found that the increase in risk remained relatively unchanged after excluding studies that did not account for smoking habits, indicating that lifestyle factors may not always be strong confounders in studies of traffic noise and CVD. Also, cohort studies with full adjustment for socioeconomic status, lifestyle, and air pollution generally find noise to be

significantly associated with coronary heart disease (39,40). Although house prices are known to be negatively associated with traffic noise, studies have indicated that the association between traffic noise and socioeconomic status may not always be pronounced, because living in city centers of large metropolitan areas is popular, attracting residents with high socioeconomic status (41,42).

In 2011, a large cohort study found a 14% significant higher risk of incident stroke for every 10 dB(A) increase in road traffic noise (day-evening-night equivalent noise level A-weighted) (43). As for coronary heart disease, this risk increase was independent of adjustment for air pollution. This result was later confirmed by 2 large studies from London on aircraft (44) and road traffic noise (45). Both daytime and nighttime aircraft noise above 55 dB(A) significantly increased risk for stroke hospitalization with, respectively, 8% and 29% when compared with levels below 50 dB(A) in a population of 3.6 million people living around Heathrow airport (44), which suggests that nighttime noise may be especially hazardous. Similarly, based on 8.6 million residents of London, road traffic noise was found to significantly increase risk for stroke hospitalization (45). In further support, recent large population-based studies showed that traffic noise from roads and aircrafts was associated with higher stroke mortality (38,44,45). Two studies have addresses different subtypes of stroke, and both found traffic noise to be associated with ischemic stroke and not hemorrhagic stroke (38,46), which is as expected given the potential mechanisms.

Traffic noise may also result in heart failure and atrial fibrillation (37,38,47). Two large population studies of 0.75 and 4.41 million persons, respectively, found both road traffic and aircraft noise to significantly increase risk for heart failure, ranging from 2% to 7% increase in risk per 10-dB(A) rise, depending on study and type of exposure (38,47). Furthermore, one study found that road traffic noise increased risk for incident atrial fibrillation with 6% for every 10 dB(A), although this was not independent of adjustment for air pollution (37). This highlights an important aspect for road traffic noise, namely the correlation with air pollution. Several recent studies included adjustment for air pollution when investigating road traffic noise and CVD (38,43,45,46,48). Although the relatively high collinearity between road traffic noise and air pollution complicates the interpretation, most studies find the association between road traffic noise and CVD to be relatively independent of air pollution, which is also the conclusion of 2 recent reviews (42,49). In further support of traffic noise as an

CENTRAL ILLUSTRATION Proposed Pathophysiological Mechanisms of Noise-Induced Cardiometabolic Disease



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Noise causes annoyance and stress responses characterized by activation of the hypothalamic-pituitary-adrenal axis, inflammation, thrombosis, and altered gene expression. See text, section "Potential (molecular) mechanisms underlying noise-induced cardiovascular disease," for details. Modified/combined from Münzel et al. (73) with permission of the publisher. Copyright © 2017, Oxford University Press. Ang II = angiotensin II; AT₁ = angiotensin receptor type 1; ATM = ataxia telangiectasia mutated; eNOS = endothelial nitric oxide synthase; Fas = cell death signaling molecule (CD95); FOXO = Forkhead box O; HPA = hypothalamic-pituitary-adrenal; iNOS = inducible nitric oxide synthase; NADPH = nicotinamide adenine dinucleotide phosphate; Nox = NADPH oxidase; NO = nitric oxide; O₂ = oxygen; TGF = transforming growth factor.

FIGURE 3 Environmental Sources of Noise and Respective Sound Pressure Levels



independent risk factor for CVD, aircraft and railway noise, which correlates much less with air pollution than road traffic noise, have also been associated with increased risk for CVD (38,44).

NOISE AND CARDIOVASCULAR RISK FACTORS. The most comprehensively studied risk factor for CVD in a noise context is hypertension. In 2012, a meta-analysis of 24 studies showed that a 5-dB(A) rise in road traffic noise was associated with a significant odds ratio for prevalent hypertension of 1.034 (50). The meta-analysis was based on cross-sectional studies, which limits the interpretation regarding causality. However, studies on incident hypertension are emerging, largely showing that traffic noise is associated with hypertension, thereby supporting the cross-sectional findings (51-53). Also, stronger associations with hypertension have been observed for indoor noise as compared with outdoor noise (54). In further support, a large population study found aircraft, railway, and road traffic noise to be associated with hypertensive heart disease (47). An important tool when evaluating causality is intervention studies. But for noise and CVD such studies are rare, as evidenced by a recent World Health Organization review, identifying only 4 relevant studies of noise and CVD (55) (Figure 3). These were all cross-sectional hypertension studies, and although 3 studies indicated changes with a quiet side, the last study found no effect.

Other important biologic risk factors for CVD have also been associated with exposure to traffic noise. In 2014, nighttime road traffic noise was found to significantly increase the thoracic aortic calcification burden, a recognized marker of atherosclerosis, by 3.9% for every 5-dB(A) increase, among 4,800 participants (48). Also, road traffic noise was significantly associated with increased heart rate in a cohort of 88,000 persons (56) and the total number of noise events during the night, but not during daytime, has been associated with arterial stiffness (57). In contrast, associations between traffic noise and blood lipids and high-sensitive C-reactive protein were found to disappear after adjustment for air pollution (58).

Recently, several studies have almost consistently found associations between aircraft and road traffic noise and obesity, a major risk factor for CVD, in cross-sectional and longitudinal studies of high quality (59-62). Furthermore, 3 cohort studies found traffic noise to significantly increase diabetes risk (63-65), and a recent study of 62,000 persons found road traffic noise associated with higher levels of fasting glucose (58). As a consequence of stress and sleep disturbance, noise may affect other lifestyle risk factors, as indicated by recent studies showing that traffic noise was associated with physical inactivity (66,67) and possibly smoking and alcohol consumption (68).

TABLE 1 Noise-Abatement Approaches

Abatement Procedures	Reduction in Noise, dB	Cost-Effectiveness Score (1-5)*
Noise barriers	3-20	2
Brake blocks for trains	8-10	4
Building insulation	5-10	1
Building design	2-15	3
Changing driving styles	5-7	3
Quiet road surfaces	3-7	5
Low-noise tires	3-4	3
Land-use planning and design	Unknown	4
Electric cars	1	1
Traffic management	3	3

*Evaluated by the European Commission in "10 ways to combat noise pollution" (70). Lowest score = 1; highest score = 5.
dB = decibel.

In conclusion, more and more large studies of high quality find that traffic noise is associated with coronary heart disease and stroke, as well as with major risk factors for CVD, most importantly hypertension and metabolic disease.

MITIGATION STRATEGIES. High exposure to transportation noise is frequent in modern societies, with more than 30% of the European population being exposed to residential day-evening-night equivalent noise level A-weighted levels above 55 dB(A) (69) (Figure 3). This leads to a considerable increase in incidence and mortality of major CVD (69), and therefore development of mitigation strategies is highly important. A large number of different noise abatement approaches are available, as recently summarized by the European Commission (Table 1) (70).

Noise insulation of buildings is effective in reducing exposure to all outdoor noise sources, but is associated with low cost-effectiveness because of high costs of implementation. New technologies and improvements are important contributions in reducing noise levels for all transportation noise sources (e.g., development of quieter engines, low-noise tires for vehicles, and low-noise brake blocks for trains). Road traffic is by far the greatest contributor to traffic noise pollution, and frequently used abatement procedures are reduced speed limits, quiet road surfaces, and noise barriers along major roads. However, because of the extent and the temporal increase in exposure, other strategies, such as traffic management and regulation and development of low-noise tires, are greatly needed. Air transport has increased for many years, and strategies for reducing exposure include restriction or curfew during night, where noise has been shown to be especially

hazardous (13,48,51). However, exposure during morning, daytime, and evening is also detrimental to health, and other strategies are needed (e.g., changing the descent procedure and limiting running of engines on the ground) (70).

Thus, because the percentage of the population exposed to detrimental levels of transportation noise is rising, new developments and legislation to reduce noise are important for public health.

POTENTIAL (MOLECULAR) MECHANISMS UNDERLYING NOISE-INDUCED CVD. Based on the epidemiological evidence and mechanistic insight from translational human and animal data, we propose that noise induces a stress response, characterized by activation of the sympathetic system and increased levels of catecholamines, cortisone, and angiotensin-II, which initiates sequelae, ultimately leading to vascular damage (Central Illustration) (5). Angiotensin II is a potent activator of the vascular and phagocytic NADPH oxidase, which can lead to oxidative stress in the blood and the vasculature. Reactive oxygen species scavenge nitric oxide and cause endothelial nitric oxide synthase (eNOS) uncoupling through oxidation of the eNOS cofactor tetrahydrobiopterin and eNOS S-glutathionylation, thereby further increasing vascular oxidative stress (71). At the level of gene regulation, reactive oxygen species impair signaling pathways centered around phosphatidylinositol 3-kinase/protein kinase B, the Forkhead box O transcription factors, transforming growth factor- β 1, and nuclear factor- κ B, all of which lead to activation of the endothelin-1 system, increased levels of circulating interleukin-6, and higher expression of vascular adhesion molecules. Oxidative stress goes hand in hand with increased inflammation (72). Immune cells (neutrophils, natural killer cells, and monocytes/macrophages) produce higher amounts of superoxide and nitric oxide on infiltration into the vasculature ultimately leading to oxidative protein modifications, such as 3-nitrotyrosine, malondialdehyde, and 4-hydroxynonenal, and adverse redox-regulatory effects on cellular signaling pathways. Higher circulating and tissue glucocorticoid levels contribute to a further reduction of endothelial nitric oxide production, marked impairment of vasodilation, and increased blood pressure. Constrictive pathways are activated by the increased levels of catecholamines and endothelin-1 as well as cross-activation by glucocorticoids. The adverse vascular alterations may contribute to the development of arterial hypertension, coronary artery disease, heart failure, and metabolic disorders (Central Illustration).

SUMMARY AND CONCLUSIONS

The presented evidence further strengthens the concept that transportation noise per se contributes to the development of cardiovascular risk of coronary artery disease, arterial hypertension, stroke, and heart failure.

With regard to understanding the pathophysiological mechanisms, a growing body of evidence finds that noise is associated with oxidative stress, vascular dysfunction, autonomic imbalance, and metabolic abnormalities, potentiating not only the adverse impact of cardiovascular risk factors, such as arterial hypertension and diabetes, but also contributing to the progression of atherosclerosis and increased susceptibility to cardiovascular events.

Thus, there is increasing rationale for studying the interaction between this novel risk factor and

its collective impact on cardiometabolic diseases. The questions that need to be addressed are many and include the magnitude and time course of response to coexposure of noise and air pollution; synergistic effects of both exposures on surrogate measures, such as blood pressure and metabolic risk; duration of effect/time course of reversal; impact of low-grade background noise exposure on air pollution exposure effects and vice versa; impact of noise on the circadian rhythm; and finally the effects on lifestyle (e.g., diet, stress, and exercise).

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REFERENCES

1. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2224–60.
2. Münzel T, Gori T, Babisch W, Basner M. Cardiovascular effects of environmental noise exposure. *Eur Heart J* 2014;35:829–36.
3. Münzel T, Sorensen M, Gori T, et al. Environmental stressors and cardio-metabolic disease: part I—epidemiologic evidence supporting a role for noise and air pollution and effects of mitigation strategies. *Eur Heart J* 2017;38:550–6.
4. Babisch W. Cardiovascular effects of noise. *Noise Health* 2011;13:201–4.
5. Babisch W. Stress hormones in the research on cardiovascular effects of noise. *Noise Health* 2003;5:1–11.
6. Münzel T, Knorr M, Schmidt F, von Bardeleben S, Gori T, Schulz E. Airborne disease: a case of a Takotsubo cardiomyopathy as a consequence of nighttime aircraft noise exposure. *Eur Heart J* 2016;37:2844.
7. Babisch W, Pershagen G, Selander J, et al. Noise annoyance: a modifier of the association between noise level and cardiovascular health? *Sci Total Environ* 2013;452–453:50–7.
8. Babisch W, Ising H, Gallacher JE. Health status as a potential effect modifier of the relation between noise annoyance and incidence of ischaemic heart disease. *Occup Environ Med* 2003;60:739–45.
9. Beutel ME, Junger C, Klein EM, et al. Noise annoyance is associated with depression and anxiety in the general population: the contribution of aircraft noise. *PLoS One* 2016;11:e0155357.
10. Sherwood A, Hinderliter AL, Watkins LL, Waugh RA, Blumenthal JA. Impaired endothelial function in coronary heart disease patients with depressive symptomatology. *J Am Coll Cardiol* 2005;46:656–9.
11. Babisch W. Transportation noise and cardiovascular risk: updated review and synthesis of epidemiological studies indicate that the evidence has increased. *Noise Health* 2006;8:1–29.
12. Babisch W, Kamp I. Exposure-response relationship of the association between aircraft noise and the risk of hypertension. *Noise Health* 2009;11:161–8.
13. Schmidt F, Kolle K, Kreuder K, et al. Nighttime aircraft noise impairs endothelial function and increases blood pressure in patients with or at high risk for coronary artery disease. *Clin Res Cardiol* 2015;104:23–30.
14. Schmidt FP, Basner M, Kroger G, et al. Effect of nighttime aircraft noise exposure on endothelial function and stress hormone release in healthy adults. *Eur Heart J* 2013;34:3508–3514a.
15. Charakida M, Deanfield JE. Nighttime aircraft noise exposure: flying towards arterial disease. *Eur Heart J* 2013;34:3472–4.
16. Jarup L, Babisch W, Houthuijs D, et al. Hypertension and exposure to noise near airports: the HYENA study. *Environ Health Perspect* 2008;116:329–33.
17. Babisch W, Ising H, Gallacher JE, Sweetnam PM, Elwood PC. Traffic noise and cardiovascular risk: the Caerphilly and Speedwell studies, third phase–10-year follow up. *Arch Environ Health* 1999;54:210–6.
18. Haralabidis AS, Dimakopoulou K, Vignataglianti F, et al. Acute effects of night-time noise exposure on blood pressure in populations living near airports. *Eur Heart J* 2008;29:658–64.
19. Amir O, Alroy S, Schliamser JE, et al. Brachial artery endothelial function in residents and fellows working night shifts. *Am J Cardiol* 2004;93:947–9.
20. Takase B, Akima T, Uehata A, Ohsuzu F, Kurita A. Effect of chronic stress and sleep deprivation on both flow-mediated dilation in the brachial artery and the intracellular magnesium level in humans. *Clin Cardiol* 2004;27:223–7.
21. Chien KL, Chen PC, Hsu HC, et al. Habitual sleep duration and insomnia and the risk of cardiovascular events and all-cause death: report from a community-based cohort. *Sleep* 2010;33:177–84.
22. Ferrie JE, Shipley MJ, Cappuccio FP, et al. A prospective study of change in sleep duration: associations with mortality in the Whitehall II cohort. *Sleep* 2007;30:1659–66.
23. Flammer AJ, Anderson T, Celermajer DS, et al. The assessment of endothelial function: from research into clinical practice. *Circulation* 2012;126:753–67.
24. Münzel T, Daiber A, Steven S, et al. Effects of noise on vascular function, oxidative stress, and inflammation: mechanistic insight from studies in mice. *Eur Heart J* 2017;38:2838–49.
25. Vienneau D, Schindler C, Perez L, Probst-Hensch N, Roosli M. The relationship between transportation noise exposure and ischemic heart disease: a meta-analysis. *Environ Res* 2015;138:372–80.
26. Lauer AM, May BJ, Hao ZJ, Watson J. Analysis of environmental sound levels in modern rodent housing rooms. *Lab Anim (NY)* 2009;38:154–60.
27. Turner JG, Parrish JL, Hughes LF, Toth LA, Caspary DM. Hearing in laboratory animals: strain differences and nonauditory effects of noise. *Comp Med* 2005;55:12–23.
28. Peterson EA, Augenstein JS, Tanis DC, Augenstein DG. Noise raises blood pressure without impairing auditory sensitivity. *Science* 1981;211:1450–2.

29. Wu CC, Chen SJ, Yen MH. Effects of noise on blood pressure and vascular reactivities. *Clin Exp Pharmacol Physiol* 1992;19:833–8.
30. Wu CC, Chen SJ, Yen MH. Attenuation of endothelium-dependent relaxation in mesenteric artery during noise-induced hypertension. *J Biomed Sci* 1994;1:49–53.
31. Altura BM, Altura BT, Gebrewold A, Ising H, Gunther T. Noise-induced hypertension and magnesium in rats: relationship to microcirculation and calcium. *J Appl Physiol* (1985) 1992;72:194–202.
32. Said MA, El-Gohary OA. Effect of noise stress on cardiovascular system in adult male albino rat: implication of stress hormones, endothelial dysfunction and oxidative stress. *Gen Physiol Biophys* 2016;35:371–7.
33. Gannouni N, Mhamdi A, Tebourbi O, El May M, Sakly M, Rhouma KB. Qualitative and quantitative assessment of noise at moderate intensities on extra-auditory system in adult rats. *Noise Health* 2013;15:406–11.
34. Baldwin AL, Bell IR. Effect of noise on microvascular integrity in laboratory rats. *J Am Assoc Lab Anim Sci* 2007;46:58–65.
35. Cui B, Gai Z, She X, Wang R, Xi Z. Effects of chronic noise on glucose metabolism and gut microbiota-host inflammatory homeostasis in rats. *Sci Rep* 2016;6:36693.
36. Babisch W. Updated exposure-response relationship between road traffic noise and coronary heart diseases: a meta-analysis. *Noise Health* 2014;16:1–9.
37. Monrad M, Sajadieh A, Christensen JS, et al. Residential exposure to traffic noise and risk of incident atrial fibrillation: a cohort study. *Environ Int* 2016;92–93:457–63.
38. Heritier H, Vienneau D, Foraster M, et al. Transportation noise exposure and cardiovascular mortality: a nationwide cohort study from Switzerland. *Eur J Epidemiol* 2017;32:307–15.
39. Roswall N, Raaschou-Nielsen O, Ketzel M, et al. Long-term residential road traffic noise and NO₂ exposure in relation to risk of incident myocardial infarction: a Danish cohort study. *Environ Res* 2017;156:80–6.
40. Selander J, Nilsson ME, Bluhm G, et al. Long-term exposure to road traffic noise and myocardial infarction. *Epidemiology* 2009;20:272–9.
41. Hjortebjerg D, Andersen AM, Christensen JS, et al. Exposure to road traffic noise and behavioral problems in 7-year-old children: a cohort study. *Environ Health Perspect* 2016;124:228–34.
42. Stansfeld SA. Noise effects on health in the context of air pollution exposure. *Int J Environ Res Public Health* 2015;12:12735–60.
43. Sorensen M, Hvidberg M, Andersen ZJ, et al. Road traffic noise and stroke: a prospective cohort study. *Eur Heart J* 2011;32:737–44.
44. Hansell AL, Blangiardo M, Fortunato L, et al. Aircraft noise and cardiovascular disease near Heathrow airport in London: small area study. *BMJ* 2013;347:f5432.
45. Halonen JI, Hansell AL, Gulliver J, et al. Road traffic noise is associated with increased cardiovascular morbidity and mortality and all-cause mortality in London. *Eur Heart J* 2015;36:2653–61.
46. Sorensen M, Luhdorf P, Ketzel M, et al. Combined effects of road traffic noise and ambient air pollution in relation to risk for stroke? *Environ Res* 2014;133:49–55.
47. Seidler A, Wagner M, Schubert M, et al. Aircraft, road and railway traffic noise as risk factors for heart failure and hypertensive heart disease: a case-control study based on secondary data. *Int J Hyg Environ Health* 2016;219:749–58.
48. Kalsch H, Hennig F, Moebus S, et al. Are air pollution and traffic noise independently associated with atherosclerosis: the Heinz Nixdorf Recall Study. *Eur Heart J* 2014;35:853–60.
49. Tetreault LF, Perron S, Smargiassi A. Cardiovascular health, traffic-related air pollution and noise: are associations mutually confounded? A systematic review. *Int J Public Health* 2013;58:649–66.
50. van Kempen E, Babisch W. The quantitative relationship between road traffic noise and hypertension: a meta-analysis. *J Hypertens* 2012;30:1075–86.
51. Dimakopoulou K, Koutentakis K, Papageorgiou I, et al. Is aircraft noise exposure associated with cardiovascular disease and hypertension? Results from a cohort study in Athens, Greece. *Occup Environ Med* 2017;74:830–7.
52. Eriksson C, Rosenlund M, Pershagen G, Hilding A, Ostenson CG, Bluhm G. Aircraft noise and incidence of hypertension. *Epidemiology* 2007;18:716–21.
53. Fuks KB, Weinmayr G, Basagana X, et al. Long-term exposure to ambient air pollution and traffic noise and incident hypertension in seven cohorts of the European study of cohorts for air pollution effects (ESCAPE). *Eur Heart J* 2017;38:983–90.
54. Foraster M, Kunzli N, Aguilera I, et al. High blood pressure and long-term exposure to indoor noise and air pollution from road traffic. *Environ Health Perspect* 2014;122:1193–200.
55. Brown AL, van Kamp I. WHO environmental noise guidelines for the European region: a systematic review of transport noise interventions and their impacts on health. *Int J Environ Res Public Health* 2017;14:E873.
56. Zijlema W, Cai Y, Doiron D, et al. Road traffic noise, blood pressure and heart rate: pooled analyses of harmonized data from 88,336 participants. *Environ Res* 2016;151:804–13.
57. Foraster M, Eze IC, Schaffner E, et al. Exposure to road, railway, and aircraft noise and arterial stiffness in the SAPALDIA study: annual average noise levels and temporal noise characteristics. *Environ Health Perspect* 2017;125:097004.
58. Cai Y, Hansell AL, Blangiardo M, et al. Long-term exposure to road traffic noise, ambient air pollution, and cardiovascular risk factors in the HUNT and lifelines cohorts. *Eur Heart J* 2017;38:2290–6.
59. Christensen JS, Raaschou-Nielsen O, Tjønneland A, et al. Long-term exposure to residential traffic noise and changes in body weight and waist circumference: a cohort study. *Environ Res* 2015;143:154–61.
60. Eriksson C, Hilding A, Pyko A, Bluhm G, Pershagen G, Ostenson CG. Long-term aircraft noise exposure and body mass index, waist circumference, and type 2 diabetes: a prospective study. *Environ Health Perspect* 2014;122:687–94.
61. Pyko A, Eriksson C, Oftedal B, et al. Exposure to traffic noise and markers of obesity. *Occup Environ Med* 2015;72:594–601.
62. Pyko A, Eriksson C, Wallas A, Ögren M, Pershagen G. Long-term exposure to traffic noise and development of obesity. 12th ICBEN Congress on Noise as a Public Health Problem. Zurich. 2017:1–7. Available at: www.icben.org. Accessed December 12, 2017.
63. Sorensen M, Andersen ZJ, Nordsborg RB, et al. Long-term exposure to road traffic noise and incident diabetes: a cohort study. *Environ Health Perspect* 2013;121:217–22.
64. Eze IC, Foraster M, Schaffner E, et al. Long-term exposure to transportation noise and air pollution in relation to incident diabetes in the SAPALDIA study. *Int J Epidemiol* 2017;46:1115–25.
65. Clark C, Sbihi H, Tamburic L, Brauer M, Frank LD, Davies HW. Association of long-term exposure to transportation noise and traffic-related air pollution with the incidence of diabetes: a prospective cohort study. *Environ Health Perspect* 2017;125:087025.
66. Roswall N, Ammitzboll G, Christensen JS, et al. Residential exposure to traffic noise and leisure-time sports: a population-based study. *Int J Hyg Environ Health* 2017;220:1006–13.
67. Foraster M, Eze IC, Vienneau D, et al. Long-term transportation noise annoyance is associated with subsequent lower levels of physical activity. *Environ Int* 2016;91:341–9.
68. Roswall N, Christensen JS, Bidstrup PE, et al. Associations between residential traffic noise exposure and smoking habits and alcohol consumption: a population-based study. *Environ Pollut* 2017 Nov 6 [E-pub ahead of print].
69. European Environment Agency. Noise in Europe 2014. EEA Report 2014;10:1–68.
70. Noise abatement approaches. Future Brief 17. Produced for the European Commission DG Environment by the Science Communication Unit, UWE, Bristol. Science for Environment Policy 2017:1–28.
71. Forstermann U, Münzel T. Endothelial nitric oxide synthase in vascular disease: from marvel to menace. *Circulation* 2006;113:1708–14.
72. Wenzel P, Kossmann S, Münzel T, Daiber A. Redox regulation of cardiovascular inflammation: immunomodulatory function of mitochondrial and Nox-derived reactive oxygen and nitrogen species. *Free Radic Biol Med* 2017;109:48–60.
73. Münzel T, Sorensen M, Gori T, et al. Environmental stressors and cardio-metabolic disease: part II-mechanistic insights. *Eur Heart J* 2017;38:557–64.

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