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September 6, 2018

By Electronic Delivery
U.S Mail to Follow

Ted Anasis, Manager
Airport Planning
San Diego County Regional Airport Authority
3225 North Harbor Drive, 3rd Floor
San Diego, CA 92101
planning@san.org

Re: San Diego International Airport Development Plan Draft Environmental Impact Report

Dear Mr. Anasis:

This firm represents Quiet Skies La Jolla, Inc. ("QSLJ"), which is a non-profit 501(c)(4) entity, whose purposes include, among other things, advocating for La Jolla's interests with respect to noise associated with the FAA's implementation of NextGen Metroplex and related commercial air operations, and the proposed expansion of San Diego International Airport ("SDIA") as described by the Airport Authority in the Draft Environmental Impact Report ("DEIR"). QSLJ is not opposed to expansion of the SDIA, but believes it should be smart and informed growth, and thoroughly evaluated in the context of all circumstances and potential adverse impacts. The proposed airport expansion should be accompanied by sufficient mitigation efforts to address the noise, health and related impacts to La Jolla, its residents and other communities. The DEIR inadequately addresses the serious concerns that would be associated with the increased commercial air traffic accompanying the expansion and the implementation of the NextGen Metroplex project.[1]

[1] As an additional matter, the use of security-related technology making it impossible to accurately "copy and paste" excerpts of the EIR caused the process of review and accurate citation to various portions of the EIR to be very difficult. On August 16, 2018, this office sent a letter to Anthony Skidmore, EIR Project Manager and requested that the EIR be reposted without the offending security code. (See Exhibit A.). Although I received a copy of the EIR without a security code preventing accurate copying and pasting on September 1st, no doubt the vast majority of the public attempting to comment on the EIR were frustrated by the inability to copy and paste relevant portions of the lengthy EIR that were of interest to them.

Although the EIR does not give a clear description of the magnitude of the proposed expansion project, according to news reports, it is a $3 billion project which would add at least eleven gates, increasing existing Terminal One from nineteen to thirty gates. In a proposed second phase of the project, which would not be completed until 2035, Terminal 2 would undergo several further improvements, including modernizing the older eastern portion of the terminal. The net effect of the planned changes would be to expand SDIA's capacity by increasing the total gates from the current fifty-one to sixty-one, all of which could accommodate wide-bodied jets, carrying more passengers and heavier loads.

The DEIR further discloses that the project would add significant commercial space, a 7,500 car parking structure, a dual-level roadway in front of the terminal and a new airport entry road near the intersection of Laurel Street and North Harbor Drive.

QSLJ's primary focus on this proposed project is the anticipated increase in noise from a greatly expanded airport, both in terms of the number and size of the planes, with consequent increases in the noise impacts to at least the Bird Rock, Upper and Lower Hermosa, La Jolla Shores, Downtown and Muirlands areas of La Jolla that have been dramatically and adversely impacted by the implementation of the Next Gen/Metroplex project in November 2016 and March 2017.

The DEIR fails to deal with these issues and many others. As a result, the DEIR is fatally flawed should be revised and republished for public comment.

QSLJ's concerns regarding noise impacts include at least the following:

1) The failure of the EIR to clearly address the increased air traffic issue by, for example, addressing and disclosing the number, frequency and size of the contemplated additional aircraft flights projected to be associated with the airport expansion; QSLJ anticipates that there will be many more flights each day and that those flights will be serviced by larger, and potentially noisier aircraft, further increasing the burden on La Jolla and other communities surrounding SDIA.

2) The lack of evidence to support the DEIR's repeated but irrational blanket assertion that there will be no increase in air traffic beyond that which would occur without completing the expansion project;

3) The failure to clearly identify, disclose and assess the magnitude of the additional anticipated noise burden associated with the airport expansion project and NextGen MetroPlex, beyond that historically considered in the airport's immediate 65 CNEL impact zone, which excludes La Jolla and other nearby communities;

4) The exclusive use of Community Noise Equivalent Level **(**CNEL) to determine noise impacts, which is based upon an averaging of noise throughout a day, and the failure to conduct an analysis of single event noise levels (SENL), which is required by CEQA when there is evidence of a significant impact from noise from individual flights;

5) The failure to consider, disclose, address and assess the impact of the additional aircraft associated noise on human health, including, without limitation, sleep diminution and/or deprivation;

6) The assertion that there is no "definitive" evidence of adverse health impacts from noise, despite substantial evidence to the contrary; and

7) The assertion that the impacts cannot be mitigated beyond what can generally be provided through sound insulation in the historic impact area immediately surrounding the airport when there are other feasible mitigation measures, including those proposed by QSLJ in connection with the Airport Authority's Flight Path & Procedures Study, and the Part 150 Study.

A) The EIR Fails To Clearly Identify The Number, Kinds And Frequency Of Additional Flights That Are Projected In Connection With The Proposed Airport Expansion.

The number of commercial aircraft noise complaints from La Jolla and other communities has dramatically spiked since the implementation of NextGen Metroplex in March of 2017.[2] Noise associated with the new flight paths and procedures under NextGen Metroplex has substantially interfered with La Jolla residents' quiet enjoyment of their properties and the open space of La Jolla. Existing aircraft noise has generated thousands of complaints and diminished quality of life historically enjoyed in La Jolla. The contemplated expansion would substantially aggravate that adverse impact unless noise is mitigated by adjusting flight paths and procedures in, around, over and adjacent to La Jolla.

To fairly evaluate the likely impact of noise levels associated with the project, two baselines should be analyzed: the noise levels before implementation of the Next Gen

[2] It is unusual in a project of this sort that the environmental review document is not a joint Environmental Impact Report/Environmental Impact Statement under the auspices of both the Airport Authority and the FAA. It would have been useful if the DEIR had explained what is contemplated in terms of FAA review, and whether the status of the Next Gen project may have influenced the decision. In any case, concerns about delay that may be caused by the need to prepare a Revised DEIR should be diminished due to the fact that the project cannot commence without FAA review, which is contingent upon review under NEPA.

Metroplex project and those which have occurred since Next Gen Metroplex was implemented. Once those baselines are established, further analysis is required to project the increase in noise associated with the DEIR expansion project, including but not limited to analysis of the number of daily flights and types of aircraft projected at various times of the day at various stages of project implementation. Currently, there is no discussion in the DEIR addressing the number of flight operations at SDIA each day, nor are there any projections addressing the number of additional flights that SDIA could accommodate with the expansion project. We understand from other reports that have been submitted by the Airport Authority that there are currently approximately six hundred and forty flights per day at SDIA. The DEIR is silent regarding the number of projected flight operations after contemplated expansion and build-out.

B) There Is No Evidence To Support The DEIR's Repeated Assertion That There Will Be No Increase In Air Traffic Beyond That Which Would Occur Without The Project.

The DEIR's assertion that aviation activity at the airport would grow at exactly the same rate as is currently projected without the Project (DEIR at 3.15-55, et seq.) is not a reasonable assumption. If the airport remains in its current state with respect to the number of gates and facilities, the number of flight operations and travelers per day will be fewer than if the facilities and gates are expanded and increased. Further, many of the existing gates are too narrow to accommodate wide body long haul aircraft, and adding wider gates would enable airlines to increase throughput at SDIA. Those additional and larger aircraft will have an impact on the noise and health burdens imposed on surrounding communities, including La Jolla. Accordingly, the DEIR should address the increased capacity and its impact on the surrounding communities. To facilitate an increase in flights and passengers is obviously the reason for the expansion, or the Airport Authority would not contemplate investing approximately $3 billion to implement the project. Yet the DEIR contains no projection of the number or types of planes that can reasonably be expected after the airport expansion, even though this is a key factor in determining many of the project's impacts, especially noise.

C) The EIR Fails To Clearly Analyze The Scope Of The Increases In Noise In Areas Beyond Those Historically Considered In The Airport's Immediate Impact Zone, Which Is Primarily East Of The Airport And Westerly Over Ocean Beach. The DEIR Should Study The Impacts Of Departures And Arrivals On La Jolla And Other Communities.

There have been numerous hearings of the Airport Noise Subcommittee regarding the increase in noise in La Jolla since the implementation of the Next Gen Metroplex project, and the Airport Board has authorized a new Flight Path and Procedure Study, plus a new Part 150 study to analyze the noise levels that are currently being experienced.

Exhibit B is the chart summarizing the number of complaints recorded by Airnoise users by hour of the day and Exhibit C shows complainants by zip code. In addition to these data, the Airport Authority has many other resident and citizen complaints from those who go to the Airport Authority's website complaint system. All that information should be compiled and included in the Revised DEIR to show the baseline of the noise problem by communities.

With regard specifically to La Jolla, the Airport Authority's own noise consultant, who examined the impacts of (and noise complaints regarding) implementation of the Next Gen Metroplex project, observed at one of the Advisory Committee meetings that La Jolla has a unique topography resulting in amplified noise off the hills and ocean, and that the duration of noise events here can be very long - as much as 90 seconds. The consultant further noted that La Jolla is exposed to both departing and arriving flights - leading to periods of near constant commercial aircraft noise. Accordingly, La Jolla is subjected to near constant new commercial aircraft noise, where it traditionally has been an extremely quiet community, unaffected by commercial aviation. Because of its overall low ambient noise level, the noise from planes is even more noticeable.

The DEIR must study the impact of the additional noise associated with the NextGen Metroplex implementation and the proposed expansion of SDIA, and mitigation efforts must be implemented to protect the residents of La Jolla from unnecessary noise.

D) The Exclusive Use Of Community Noise Equivalent Level (CNEL) To Determine Noise Impacts, Which Is Based Upon An Averaging Of Noise Throughout A Day, Is Improper. An Analysis Of Single Event Noise Levels (SENL) Is Required Under Relevant CEQA Case Law Because There Is Evidence Of A Significant Impact From Noise From Individual Flights And Adverse Impacts To Community Residents.

The noise analysis in the DEIR is all based upon Community Noise Equivalent Exposure Level (CNEL), which reflects the average day's noise from the airport. "CNEL metric used for this aircraft noise analysis is based on an Average Annual Day (AAD) of aircraft operations." (3.12-5.) As the County Noise Guidelines state: "In the case of airport or aircraft noise, CNEL is often expressed as a 365-day average." While this information is the protocol used by the FAA, and is certainly of interest, it is not sufficient.

In a closely analogous situation to that which is before the Airport Authority, residents of Alameda County and specifically residents of the City of Berkeley expressed concern about the proposed expansion of San Francisco International Airport because of ongoing noise problems. Like here, even though testing in their communities showed that the CNEL noise levels were below 65 dB based upon a CNEL analysis, residents

expressed their opinions about the interference with communications, conversation, work and sleep based upon the overflight of individual jets. The Court of Appeal concluded CEQA "imposes its own requirements for assessing environmental impacts from noise" and that a single event analysis is required when there is evidence of a significant adverse noise impact to a community from commercial air traffic. *Berkeley Keep Jets Over the Bay Committee v. Board of Port Commissioners* (2001) 91 Cal.App.4th 1344 at 1379-82.

The court in *Berkeley Jets* relied heavily upon the case of *Davison v. Department of Defense I*, (S.D. Ohio, 1982) 560 F. Supp 1019. In that case the plaintiffs challenged the sufficiency of an EIS prepared under the National Environmental Policy Act in connection with the addition of civilian air cargo operations at Rickenbacker Air National Guard Base. According to the federal court, the "greatest single environmental impact" occasioned by the proposed nighttime air cargo flights was on the sleep of the people who lived near the airfield. (*Id.* at p. 1033.) The *Davison* court cited several technical deficiencies in the EIS. First, the study did not state the number of night flights that traditionally had taken off or landed at the airfield. (560 F.Supp. at p. 1037.) Second, it did not estimate the number of times a nearby resident could be awakened by overflights during "normal" or "worst case" nights. Third, the study did not discuss whether residents' sleep disturbance would diminish over time. Finally, the EIS did not address the issue of whether long-term exposure to noise-induced sleep disturbance would result in any important physiological effects. The court pointed out that because these issues would be vital considerations to a decisionmaker analyzing the proposal, the EIS did not meet NEPA's mandate to explore unavoidable environmental consequences "'to the fullest extent possible.'" (*Ibid.*)

The same deficiencies exist in this Draft EIR. Those deficiencies must be corrected and the EIR must identify the number of existing flights, the projected number of flights with expansion of the airport, and an estimate the number of times a resident would be adversely impacted by "normal" and "worst case" flights.

A single event analysis is required in this DEIR, based on the many existing complaints from La Jolla residents, and surrounding communities. As drafted, the DEIR fails to satisfy the requirements of CEQA since *Berkeley Jets* stressed the need to provide information in a form that is useful to residents surrounding an airport in helping to evaluate the impact of future increased air traffic on their daily lives, in particular the interference with sleep and conversation, by individual "single events" of aircraft takeoffs and landings. (Id. at 1372-83.)

"Single event" noise is defined as the noise associated with one and only one event. (Single Event Noise Exposure Level (SENEL) or Sound Exposure Level (SEL).) The methodology of the DEIR, however, used only an averaging technique, rather than

disclosing individual "single events." The DEIR should have provided noise contours for each individual takeoff and landing over a typical period in order to provide residents with information about the noise impact, frequency, and timing of those "single events." That information would allow the public and decisionmakers to evaluate the significance of those impacts on health, sleep, conversation, and quality of life and reasonably consider what an increase in the number of planes would mean to those considerations.

E) The DEIR Is Inadequate Because Most Of The Analysis About Noise Impacts Focuses Only On The Noise Levels At Which A Sleeping Person Will Be Awakened From Sleep Rather Than Also Addressing The Sleep Interference Or Deprivation That Occurs As A Result Of The Noise From Flights In The Late Evening And Early Morning, And The Adverse Impacts From That Deprivation.

No adequate analysis has been conducted or considered with regard to the interference with schools, education and learning associated with the contemplated and existing increased noise. Analysis should also be conducted regarding interruptions and interference with communications, the home environment and work environment. While noise measurements have been provided from the schools within the traditional impact zone, there has been no analysis of the impacts on any of the public or private schools in La Jolla, such as the La Jolla elementary schools, Muirlands Middle School, La Jolla High School, and The Bishop's School. At the very least there should be an inquiry made to all of the potentially impacted schools.

However, one of the most significant impacts from the increase of the noise from flights adjacent to and around or over La Jolla is the reduction in both the quantity and quality of sleep for both adults and children. For example, attached is a Declaration of Jan Chatten-Brown, counsel for QSLJ, regarding her experiences with flight noise from the airport since the initiation of the Next Gen project. See, Exhibit D, the Declaration of Jan Chatten-Brown, which describes how she used to get eight hours of sleep a night, and now gets seven or less because of late and early morning flights, despite the use of ear plugs, keeping the windows closed except when the weather is particularly hot, and using a pillow to further muffle the sound of the planes. Also see Exhibit E, the Declaration of Anthony Stiegler on how the noise from the aircraft has diminished the quality of the lives of his entire family, interfered with normal conversations and limited outdoor activities.

The loss of sleep is a significant problem. Scientists have recently focused on the importance of eight hours of sleep. There have been numerous studies and articles detailing the serious health impacts associated with inadequate sleep time or poor sleeping conditions making sleeping difficult. In fact, the Center for Disease Control strongly recommends well over eight hours of sleep for people under 18; seven or more

hours for adults 18-60; 7-9 hours for adults 61-64; and 7-8 hours for adults 65 and older. (See Exhibit F, a chart on how much sleep individuals in various age groups should get. Additionally, the New York Times reported that the CDC has "declared that sleep deprivation is a public health epidemic, with one-third of American adults getting insufficient slumber." (New York Times, p. A3, Sept 6, 2018.) And the CDC website includes a plethora of studies regarding the adverse impacts of sleep deprivation, as well as studies supporting their recommendation for the minimum amount of sleep that each age category should receive. There are even reports about airport noise. The drafters of the EIR should carefully review the CDC website to locate more information about the health effects of sleep deprivation and include that information in a Revised DEIR.

One of the primary researchers working on the health effects of the loss of sleep is Matthew Walker, Ph.D, Professor of Neuroscience and Psychology at the University of California, Berkeley, and Founder and Director of the Center for Human Sleep Science. (https//:psychology.berkeley.edu/people/matthew-p-walker) Dr. Walker has received numerous funding awards from the National Science Foundation and the National Institutes of Health, and is a Kavli Fellow of the National Academy of Sciences.

Dr. Walker points out that lack of sleep can have serious consequences. Sleep deficiency is associated with problems in concentration, memory and the immune system, and may even shorten life span. Dr. Walker has stated:

> "Routinely sleeping less than six or seven hours a night demolishes your immune system, more than doubling your risk of cancer. Insufficient sleep is a key lifestyle factor determining whether or not you will develop Alzheimer's disease. Inadequate sleep—even moderate reductions for just one week—disrupts blood sugar levels so profoundly that you would be classified as pre-diabetic. Short sleeping increases the likelihood of your coronary arteries becoming blocked and brittle, setting you on a path toward cardiovascular disease, stroke, and congestive heart failure." (https://www.npr.org/books/titles/558061359/why-we-sleep-unlocking-the-power-of-sleep-and-dreams#excerpt)

Further, as noted by Robert Stickgold, director of the Center for Sleep and Cognition at Harvard Medical School, "It seems as if we are now living in a worldwide test of the negative consequences of sleep deprivation." Robert Stickgold's comment appears in the August 2018 issue of *National Geographic* magazine, in an article entitled "The Science of Sleep." For the full article, click on the link: outline.com/XjHf6e.

Noise is one of the obvious conditions which can seriously impact a person's ability to have a good nights' sleep. However, impacts to healthy and sound sleep in

those persons subjected to airplane noise is not properly discussed in the DEIR, but held to be too speculative. Clearly, the authors of the DEIR have not done a thorough search of the literature.

F) The EIR Ignores Substantial Evidence Showing Adverse Health Impacts From Airport Noise In Addition To Loss Of Sleep.

The EIR asserts a relationship between noise and health effects is "plausible" but hasn't been proven. (3.12-10.) The EIR goes on to acknowledge that people exposed to noise experience higher rates of hypertension but claim that "the empirical evidence doesn't yet support a reliable prediction of noise-induced sleep disturbance." (3.12-10.) The DEIR asserts that various studies it does reference concluding noise leads to adverse health impacts are not sufficiently conclusive (3.12-11) and contends health impacts are "too speculative" to require that they be analyzed, citing CEQA Guidelines Section 15145. The failure to analyze the health impacts of airplane noise because those health impacts are "too speculative" calls to mind how, until recently, it was not uncommon for EIR's to declare climate change "too speculative," even though the vast majority of the scientific community believes it is very real. As with the impacts of climate change, the serious health consequences of an increase in commercial aircraft noise on residents of La Jolla and other communities must be analyzed.

Attached as Exhibits G and H are two important studies analyzing the significant adverse health impacts of airplane noise exposures. Here are the conclusions those studies:

1. <u>NOISE ANNOYANCE IS ASSOCIATED WITH DEPRESSION AND ANXIETY IN THE GENERAL POPULATION — THE CONTRIBUTION OF AIRCRAFT NOISE Authored By Manfred E. Beutel, Claus Junger, Eva M. Klein, Phillip Wild, Karl Lackner, Maria Blettner, Harald Binder, Matthias Michal, Jorg Wiltink, Elmar Brahler, And Thomas Munzel. Editor: Miguel A Andrade-Navarro, Johannes-Gutenberg University of Mainz, Germany. Published: May 19, 2016. Copyright: © 2016 Beutel et al.</u>

A study with 15,010 participants, conducted from April, 2007 to April, 2012, found that depression and anxiety are increased corresponding with the degree of overall noise annoyance. It discusses the fact that numerous studies show noise contributes to the following physical impacts:

- Sleep disturbance
- Development of hypertension

- Ischemic heart disease
- Heart failure
- Arrhythmia
- Metabolic syndrome
- Stroke
- Emotional difficulties in children.

Noise annoyance also causes increased risk for depression and anxiety disorders.

Further, this study shows that, in general, aircraft noise has been found to be more annoying, and with stronger effects on sleep, than road or railway noise. The degree of annoyance was from the highest to the lowest for the following exposures: Aircraft noise; road traffic; neighborhood outdoor noise; indoor noise; railway noise and industrial noise. Interestingly, aircraft noise is the leading source of extreme annoyance, and that annoyance is associated with depression and anxiety disorder (induces stress).

2. ENVIRONMENTAL NOISE AND THE CARDIOVASCULAR SYSTEM, Authored By Thomas Munzel, Md, Frank P. Schmidt, Md, Sebastian Steven, Md, Johannes Herzog, Md, Andreas Daiber, Phd, Mette Sorensen, Phd, And Published In The Journal Of The American College Of Cardiology, Journal of the American College of Cardiology, Vol. 71, No. 6, 2018. Published by Elsevier on Behalf of The American College of Cardiology Foundation.

This study concludes that noise generally is associated with: annoyance; stress; sleep disturbance and impaired cognitive performance; arterial hypertension; myocardial infarction; heart failure; and stroke.

It also concludes night time noise increases are associated with higher levels of stress hormones and vascular oxidative processes. Both of these conditions may lead to endothelial dysfunction and arterial hypertension.

Aircraft noise is specifically associated with oxidative stress-induced vascular damage, while general traffic noise (aircraft, road, and railway) is associated with increased risks of cardiovascular and metabolic diseases.

Nocturnal aircraft noise is associated with endothelial dysfunction and decreased sleep quality. It increases blood pressure.

> Reactions to aircraft noise vary by characteristics of the noise depending upon the pattern, frequency, exposure time, and intensity of the noise.
>
> 2015 studies show increased health risks with noise starting as low as 50 dB(A). Both daytime and nighttime aircraft noise above 55 resulted in significantly increased risk for stroke hospitalization. Aircraft and road traffic noise is also associated with obesity, a major risk factor for cardiovascular disease. It also presents a significantly increased risk of diabetes.

These two studies others showing the health effects of noise should be addressed in preparing the DEIR's analysis of the health impacts of expanded aircraft operations .

When there is conflicting evidence, an EIR should include a discussion of both perspectives. And when dealing with an issue of public health, the DEIR should follow the precautionary principle. At the very least, the Airport knows that the noise creates a significant negative impact on the quality of life of San Diego residents.

G. The Assertion That Noise Impacts Cannot Be Mitigated Beyond Those That Generally Provided Through Sound Insulation in the Historic Impact Area Immediately Surrounding the Airport Cannot Be Supported Because There Are Feasible Mitigation Measures That Could Dramatically Reduce Adverse Noise Impacts of Flights To and From SDIA on La Jolla. The Study Commissioned By QSLJ Conducted By ABXx2 Should Be Studied And Its Recommendations Adopted.

CEQA, unlike NEPA, mandates that impacts must be mitigated if it is possible to do so through the adoption of feasible mitigation measures or alternatives. Specifically, Public Resources Code sections 21002 and 21081(a) require that public agencies not approve projects with significant adverse environmental effects unless feasible mitigation for those effects has been adopted.

In this instance, such mitigation measures have already been recommended to the Airport Authority, and provided for analysis in the EIR, by Anthony M. Stiegler of QSLJ. QSLJ commissioned a study on flight path and procedure modifications to dramatically reduce and mitigate the increased noise impacts on La Jolla associated with the Nextgen Metroplex implementation. A copy of that study, prepared by noise experts ABCx2, has already been submitted into the record by Anthony Stiegler, one of the founders of Quiet Skies, and should be reviewed for evaluation of the feasibility of implementing the recommendations in order to mitigate the impacts of the increase in air traffic, as well as the current adverse impacts from operation of the airport on La Jolla and other communities.

We realize that the FAA would be required to consent to changes of flight paths and procedures to reduce the adverse noise impact on La Jolla and other newly impacted communities. However, based upon this firm's experience in dealing with the environmental impacts of expansion of Los Angeles International Airport, we are confident that a serious request from the Airport Authority for approval of such modified flight paths and procedures would be well received. Indeed, this alternative would also need to be studied in the Environmental Impact Statement (EIS) that will be prepared by the FAA.

H. Non-Noise Issues

While concerns about noise are the focus of this letter, we also believe there are many other aspects of the DEIR that are profoundly inadequate and must be addressed. The letter prepared on behalf of the Cleveland National Forest Foundation details many of those in adequacies, including but not limited to the following:

1. The DEIR fails to consistently define and describe the project, both in terms of completion dates and the purpose and scope of the extensive "commercial development" that is envisioned as part of the project.

2. The DEIR fails to analyze the air emissions that would result from the construction of the project and fails to propose mitigation measures.

3. Th DEIR fails to analyze the substantial increase of vehicular emissions resulting from the construction of an excessive number of new parking spots. It also fails to commit meaningfully to implementing a plan to increase non-single occupant vehicle transport to the airport, including by use of public transit (including extension of the trolley system), use of buses from remote locations to transport passengers (as are available in the Fly-Away buses in Los Angeles) or the various privately operated (but likely airport facilitated) buses from remote locations that are widely used in the Bay Area; and increasing bike and walking access to the airport for both passengers and those working at the airport.

4. The DEIR fails to identify and propose enforceable and effective mitigation measures.

While all of these other concerns are being addressed, the DEIR can be revised to clearly and objectively analyze the issues raised by QSLJ.

Conclusion

Thank you for your attention to these important matters. The DEIR addresses an important project in San Diego, but is inadequate in its current condition and detail. A thorough analysis is required. We look forward to reviewing a Revised DEIR with the necessary information identified above.

Very Truly Yours,

Jan Chatten-Brown

Enclosures:
Exhibit A - August 16, 2018 letter to Anthony Skidmore
Exhibit B - Airnoise Complaints by Time
Exhibit C - Airnoise Complainants by Zip Code
Exhibit D - Declaration of Jan Chatten-Brown
Exhibit E - Declaration of Anthony M. Stiegler
Exhibit F - How Much Sleep Do I Need - Center for Disease Control and Prevention
Exhibit G - Noise Annoyance Is Associated With Depression And Anxiety In The General Population — The Contribution Of Aircraft Noise
Exhibit H - Environmental Noise And The Cardiovascular System

EXHIBIT A

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August 16, 2018

Anthony Skidmore
EIR Project Manager
San Diego International Airport
Airport Development Plan
P.O. Box 82776
San Diego, California 92138-2776

Re: Airport Development Plan – Draft Environmental Impact Report

Dear Mr. Skidmore:

Chatten-Brown & Carstens is reviewing the Airport Draft EIR on behalf of Quiet Skies, a La Jolla group particularly concerned about airport noise and its impacts on La Jolla residents.

The California Environmental Act has been a major focus of my law practice for over 46 years, and Chatten-Brown & Carstens has been deeply involved with CEQA since its founding. Since EIR's first became available electronically, I have reviewed many EIR's on line. It is very helpful to be able to copy and paste portions of the EIR into our notes in order to assure accuracy in the depiction of the contents of the EIR. This is the first EIR that I have found which has a security provision that precludes the ability to make accurate copies of excerpts, even with OCR.

Because the very purpose of CEQA is to encourage public review and participation in the decisionmaking process, such a security provision is contrary to the policies behind CEQA. Therefore, we ask that the EIR be reposted without the security codes imbedded that prevent copying so that we may complete review and provide timely comments on it.

Thank you for your assistance in this matter.

Very truly yours,

Jan Chatten-Brown

EXHIBIT B

Airnoise Complaints by Time

	Hours	Complaints
1	Midnight	373
2	1:00 AM	118
3	2:00 AM	59
4	3:00 AM	83
5	4:00 AM	80
6	5:00 AM	83
7	6:00 AM	9643
8	7:00 AM	10818
9	8:00 AM	7790
10	9:00 AM	5384
11	10:00 AM	7506
12	11:00 AM	6831
13	12:00 PM	6287
14	1:00 PM	6281
15	2:00 PM	5736
16	3:00 PM	6033
17	4:00 PM	6635
18	5:00 PM	6320
19	6:00 PM	6542
20	7:00 PM	7533
21	8:00 PM	6864
22	9:00 PM	7477
23	10:00 PM	8709
24	11:00 PM	3012

EXHIBIT C

Airnoise Complainants
by Zip code

Zip Code	Complainants
91932	151
91941	411
91978	5141
92014	35
92037	75054
92102	1
92106	5588
92107	38793
92109	993
92114	2
92115	18
92116	2
92169	4
94513	3

EXHIBIT D

DECLARATION OF JAN CHATTEN-BROWN REGARDING NOISE IMPACTS

1. My name is Jan Chatten-Brown and I reside at 322 Bird Rock Ave., in La Jolla, California.
2. My husband and I moved to La Jolla after he retired and we built a LEED platinum home in the quiet neighborhood of Bird Rock, four houses from the ocean, on a hill overlooking the water.
3. Because there is a fairly constant breeze and because I am acutely aware of the need to reduce our carbon footprint, we chose not to install air conditioning, or even "future proof" the home by installing ducts for air conditioning.
4. Until the implementation of the Metroplex/Next Gen project we immensely enjoyed our home and neighborhood.
5. Throughout our married life, we have always slept with our windows open, and after our children were raised, I made it a practice to try to sleep eight hours a day, even when I was working long hours. Typically, I would go to sleep about 11 pm and arise at 7 pm.
6. Since the noise began to increase from aircraft flights from San Diego International Airport, at night I have a great deal of difficulty falling to sleep because of the noise, despite the use of ear plugs and using a second pillow over my ears.
7. We also keep our windows in our bedroom closed at night unless it is extremely hot, and rely on the fan for cooling, but it has been very unpleasant to sleep this way in the summer's heat.
8. I have begun going to sleep earlier in order to make-up for the delay in getting to sleep, but even with that, instead of being asleep from approximately 11 pm, I am frequently awake until 11:30 or later.
9. In the morning, I am usually awakened by aircraft noise around 6:15 or 6:30 am, and almost never sleep until 7 a.m.
10. Since I also get up once during the night, I am routinely sleeping well less than seven hours a night, which is considered an inadequate amount of sleep for my age.
11. The lack of sleep also has reduced my energy level and productivity of my legal work, and diminished my pleasure in living in this beautiful community.
12. I have begun reading numerous articles about the health consequences of a lack of sleep and believe this is a serious issue that must be considered by the San Diego Airport Authority in its consideration of the environmental impacts of expansion of the airport.

I declare the above is true and correct under penalty of perjury.

Executed in San Diego, California on September 5, 2018.

Jan Chatten-Brown

EXHIBIT E

My name is Anthony M. Stiegler,

1. I am a founder of Quiet Skies La Jolla, Inc., the party filing this objection and response letter. My residence is in the Lower Hermosa area of La Jolla.
2. Since inception of the NextGen Metroplex implementation in San Diego in March 2017, we have experienced a substantial diminution of quality of life and sleep caused by increased commercial air traffic noise adjacent to, near and over La Jolla.
3. For example, we cannot reasonably go to sleep until after the conclusion of air operations at SDIA, at approximately 11:00 p.m. each night. Likewise, we are regularly awakened each morning at 6:30 a.m. as soon as departures begin.
4. We are also precluded from the peaceful quiet enjoyment of our backyard at all times during the day from 6:30 a.m. to 11:00 p.m. caused by the new commercial jet traffic. The noise interferes with reading, normal conversations, lunch and dinner guest parties and the regular conduct of daily activities, by the constant interruption of commercial jet traffic passing by or over our home.

__/s/_____
Anthony M. Stiegler, Secretary of Quiet Skies La Jolla, Inc.
September 7, 2018

EXHIBIT F

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

How Much Sleep Do I Need?

How much sleep you need changes as you age.

Age Group		Recommended Hours of Sleep Per Day
Newborn	0–3 months	14–17 hours (National Sleep Foundation)[1] No recommendation (American Academy of Sleep Medicine)[2]
Infant	4–12 months	12–16 hours per 24 hours (including naps)[2]
Toddler	1–2 years	11–14 hours per 24 hours (including naps)[2]
Preschool	3–5 years	10–13 hours per 24 hours (including naps)[2]
School Age	6–12 years	9–12 hours per 24 hours[2]
Teen	13–18 years	8–10 hours per 24 hours[2]
Adult	18–60 years	7 or more hours per night[3]
	61–64 years	7–9 hours[1]
	65 years and older	7–8 hours[1]

Although the amount of sleep you get each day is important, other aspects of your sleep also contribute to your health and well-being. Good sleep quality is also essential. Signs of poor sleep quality include not feeling rested even after getting enough sleep, repeatedly waking up during the night, and experiencing symptoms of sleep disorders (such as snoring or gasping for air). Improving sleep quality may be helped by better sleep habits or being diagnosed and treated for any sleep disorder you may have.

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EXHIBIT G

PLOS | ONE

RESEARCH ARTICLE

Noise Annoyance Is Associated with Depression and Anxiety in the General Population- The Contribution of Aircraft Noise

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Abstract

Background

While noise annoyance has become recognized as an important environmental stressor, its association to mental health has hardly been studied. We therefore determined the association of noise annoyance to anxiety and depression and explored the contribution of diverse environmental sources to overall noise annoyance.

Patients and Methods

We investigated cross-sectional data of n = 15.010 participants of the Gutenberg Health Study (GHS), a population-based, prospective, single-center cohort study in Mid-Germany (age 35 to 74 years). Noise annoyance was assessed separately for road traffic, aircraft, railways, industrial, neighborhood indoor and outdoor noise ("during the day"; "in your sleep") on 5-point scales ("not at all" to "extremely"); depression and anxiety were assessed by the PHQ-9, resp. GAD-2.

Results

Depression and anxiety increased with the degree of overall noise annoyance. Compared to no annoyance, prevalence ratios for depression, respectively anxiety increased from moderate (PR depression 1.20; 95%CI 1.00 to 1.45; PR anxiety 1.42; 95% CI 1.15 to 1.74)

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Competing Interests: The authors received funding (unrestricted grant) from commercial sources Boehringer Ingelheim and PHILIPS Medical Systems. This does not alter the authors' adherence to all the PLOS ONE policies on sharing data and materials.

to extreme annoyance (PR depression 1.97; 95%CI 1.62 to 2.39; PR anxiety 2.14; 95% CI 1.71 to 2.67). Compared to other sources, aircraft noise annoyance was prominent affecting almost 60% of the population.

Interpretation

Strong noise annoyance was associated with a two-fold higher prevalence of depression and anxiety in the general population. While we could not relate annoyance due to aircraft noise directly to depression and anxiety, we established that it was the major source of annoyance in the sample, exceeding the other sources in those strongly annoyed. Prospective follow-up data will address the issue of causal relationships between annoyance and mental health.

Introduction

Noise, defined as 'unwanted sound' has gradually become increasingly acknowledged as an environmental stressor and as a nuisance [1]. Non-auditory effects of noise occur at levels far below those required to damage the hearing organ. Although people tend to habituate to noise exposure, the degree of habituation differs substantially between individuals and is rarely complete. If exposure to noise is chronic and exceeds certain levels, adverse health outcomes can be seen. Meanwhile numerous studies have shown that noise contributes to sleep disturbance, to the development of arterial hypertension, ischemic heart disease, heart failure, arrhythmia, metabolic syndrome and stroke (for review see [2]) and also to learning, respectively emotional difficulties in children [3].

According to the noise reaction model, two principal pathways are relevant for the development of adverse health effects of noise [4]. These refer to the 'direct' and the 'indirect' arousal and activation of the organism. The 'direct' pathway is determined by the instantaneous interaction of the acoustic nerve with different structures of the central nervous system. The 'indirect' pathway refers to the cognitive perception of the sound, its cortical activation and related emotional responses such as annoyance. Both, noise level and noise annoyance have been shown to be associated with cardiovascular disorders. Both reaction chains may initiate physiological stress reactions. The activation of fight–flight and defeat reactions is thought to involve subcortical regions of the brain like the hypothalamus, which has inputs to the autonomic nervous system, the endocrine, and the limbic system. If experienced chronically, stress caused by annoyance may even trigger the development of cardiovascular disease [2].

Annoyance is the most prevalent community response in a population exposed to environmental noise. Noise annoyance can result from interference with daily activities, feelings, thoughts, sleep, or rest, and may be accompanied by negative emotional responses, such as irritability, distress, exhaustion, a wish to escape the noise and other stress-related symptoms [5, 6]. Severe annoyance has been associated with reduced well-being and health, and because of the high number of people affected, annoyance contributes substantially to the burden of disease from environmental noise. It is estimated that DALYs (disability adjusted life years) from environmental noise in the Western European countries are 61,000 years for ischemic heart disease, 45,000 years for cognitive impairment for children, 903,000 for sleep disturbance, 22,000 years for tinnitus and 587,000 for annoyance solely http://www.euro.who.int/__data/assets/pdf_file/0008/136466/e94888.pdf.

While there is a clear relationship between the objective measurement of noise and annoyance, individual factors such as noise sensitivity, internal states (genetic, physiological, psychological, life style) that increase individuals' reactivity to noise in general [7] may play an important role [8].

The burden of mental disorders is quite high and disabling. Depression and anxiety disorders rank among the disorders with the strongest impact, as reflected by years lived with disability and reduced quality of life [9]. Comorbid somatic and mental disorders carry higher burdens when compared to somatic disorders without mental comorbidities and mental disorders without somatic comorbidities [10]. Central to most contemporary etiological theories is the notion that stress can initiate cognitive and biological processes that increase the risk for depression and for anxiety disorders [11]. Thus, it is surprising that the effect of noise on mental health has so far been infrequently studied in adults.

In a cross-sectional survey of residential areas stratified by aircraft noise level, [6, 12], annoyance was associated with an increase of noise level and with acute mental and physical symptoms. However, chronic symptoms were higher in the areas with comparatively lower noise level. Regardless of the level of noise, persons with high annoyance reported more mental and physical symptoms and used more psychotropic drugs, general practice and outpatient services [13]. In their review, van Kamp and Davies [7] concluded that individuals with mental disorders constitute a risk group for heightened noise sensitivity (along with chronically somatic ill, people suffering from tinnitus, shift workers, fetuses and neonates), which increases their risk for adverse health effects of noise. Preliminary studies indicated different effects of specific sources of traffic noise on attitudes and annoyance responses [14, 15]. In general, aircraft noise has been found more annoying, and with stronger effects on sleep, than road and railway noise [16]. In a large a population-based, prospective, observational single-center cohort study in the Rhine-Main-Region in western Mid-Germany we recently studied a sample of 15,010 participants drawn randomly from the local registry in the city of Mainz and the district of Mainz-Bingen [17]. Some of these areas are affected by a direct neighborhood to the Frankfurt Airport flight pattern; others are expected to be affected more by road traffic (e.g. motorways) or railway noise. With the present studies we were specifically interested in the relationship between noise annoyance and mental health by assessing total noise annoyance during day and night. In a second step we wanted to differentiate between the sources of extreme annoyance according to a broad range of sources (road, aircraft, train, industrial, neighborhood, etc.).

The specific questions we wanted to address with the current studies were:

1. Is noise annoyance in general associated with anxiety and depression?
2. How annoying are different sources of noise?

Methods

Study sample

We investigated cross-sectional data of n = 15.010 participants enrolled in the Gutenberg Health Study (GHS) from April 2007 to April 2012 [17]. The GHS is a population-based, prospective, observational single-center cohort study in the Rhein-Main-Region in western Mid-Germany. The study and its procedure have been approved by the ethics committee of the Statutory Physician Board of the State of Rhineland-Palatinate and by the local and federal data safety commissioners. Participation was voluntary and written informed consent was obtained from each subject upon entry into the study. The primary aim of the study was to evaluate and

improve cardiovascular risk stratification. The sample was drawn randomly from the local registry in the city of Mainz and the district of Mainz-Bingen. The sample was stratified 1:1 for gender and residence and in equal strata for decades of age. Inclusion criteria were age 35 to 74 years and written informed consent. Persons with insufficient knowledge of German language, or physical and mental inability to participate were excluded. Based on the interim analysis 5.8% were excluded because of the exclusion criteria. The response rate (defined as the recruitment efficacy proportion, i.e. the number of persons with participation in or appointment for the baseline examination divided by the sum of number of persons with participation in or appointment for the baseline examination plus those with refusal and those who were not contactable) was 60.3%. A total of 14.635 participants answered the noise annoyance items. Mean age was 54.9 (±11.1); 49.4% were female.

Materials and assessment

The 5-hour baseline-examination in the study center comprised evaluation of prevalent classical cardiovascular risk factors and clinical variables, a computer-assisted personal interview, laboratory examinations from a venous blood sample, blood pressure and anthropometric measurements. In general, all examinations were performed according to standard operating procedures by certified medical technical assistants

Questionnaires

Noise annoyance was assessed in analogy to Felscher-Suhr et. al. [18] by single questions in the format: "How annoyed have you been in the past years by . . ."? Six potential sources of noise annoyance (road traffic, aircraft, railways, industrial/construction, neighborhood indoor and outdoor) were separately rated "during the day" and "in your sleep". Ratings were done on a five-point scale ("not, slightly, moderately, strongly, extremely").

Depression was measured by the Patient Health Questionnaire (PHQ-9), which quantifies the frequency of being bothered by each of the 9 diagnostic criteria of Major Depression over the past 2 weeks. Responses are summed to create a score between 0 and 27 points. A PHQ-9 sum score of $\geq$ 10 was used for the definition of caseness for depression yielding a sensitivity of 81% and a specificity of 82% for any depressive disorder[19].

Generalized anxiety was assessed with the two screening items of the short form of the GAD-7 (Generalized Anxiety Disorder [GAD]-7 Scale) [20]. On the GAD, subjects rated "Feeling nervous, anxious or on edge" and "Not being able to stop or control worrying" by 0 = "not at all", 1 = "several days", 2 = "over half the days", and 3 = "nearly every day". A sum score of 3 and more (range 0–6) out of these two items indicates generalized anxiety with good sensitivity (86%) and specificity (83%). Both the GAD-7 and GAD-2 have been shown to perform well as screening tools for all anxiety disorders [20].

Computer-assisted personal Interview

During the computer-assisted personal interview participants were asked whether they had ever received the definite diagnosis of any depressive disorder (medical history of lifetime diagnosis of any depressive disorder, MH of Depression) by a physician. The socioeconomic status (SES) was defined according to Lampert's and Kroll's scores with a range from 3 to 27 (3 indicates the lowest SES and 27 the highest SES) [21].

Statistical analysis

Variables were reported as absolute numbers, percentages or means with standard deviations or medians with 25th and 75th percentiles as appropriate. As we were interested in total noise annoyance, we used the highest annoyance rating of all categories of noise (aircraft, road traffic, etc.) as an indicator of overall noise annoyance, regardless of whether it affected daytime or sleep. Comparisons between groups were done with Cochran-Armitage test for trend for categorical variables and with Jonckheere-Terpstra test for continuous variables as appropriate. To investigate the association between overall annoyance and depression (PHQ-9 $\geq$10), respectively generalized anxiety (GAD-2 $\geq$3) multiple generalized linear models with a binominal distribution and a log link function adjusted for sex, age and socioeconomic status were used. All reported *p*-values corresponded to 2-tailed tests. As this is an explorative study no adjustments for multiple testing have been done. *P*-values were given for descriptive reasons only. Due to the large number of tests, *p*-values should be interpreted with caution and in connection with effect estimates. Statistical analyses were performed using SAS for Windows 9.4 TS Level 1M1 (SAS Institute Inc.) Cary, NC, USA.

Results

Table 1 shows depression and anxiety according to degree of noise annoyance. Of the study participants, 20.7% reported no, 26.6% slight, 25.0% moderate, 17.3% strong, 10.5% extreme annoyance by noise. Mean depression and anxiety scores increased steadily from 3.5 to 5.1, respectively 0.7 to 1.1, with the degree of annoyance. The rates of clinically significant anxiety (GAD-2$\geq$3) and depression (PHQ-9$\geq$10) and medical diagnoses of depression, respectively anxiety, also increased steadily.

In order to determine the associations between noise annoyance, depression and anxiety, we performed a logistic regression controlling for sex, age and socioeconomic status (Fig 1). Compared to no annoyance, the odds ratio for depression increased steadily starting from moderate (1.22; 95%CI 1.00 to 1.49) to extreme annoyance, which had a 2.12 fold (95%CI 1.71 to 2.64) likelihood of depression. Correspondingly, the likelihood of anxiety increased from moderate (1.45fold; 95% CI 1.16 to 1.81) to extreme annoyance (2.28 fold; 95% CI 1.79 to 2.91).

As Fig 2 shows, the degree of annoyance was highest due to aircraft noise (affecting 59.9% of the population to some degree and 6.4% extremely), followed by road traffic (43.5%; 1.9%),

Table 1. Depression and anxiety according to the extent of total noise annoyance.

	No		*Slight*		*Moderate*		*Strong*		*Extreme*		*p*-value
	n = 3024 (20.7%)		*n = 3895 (26.6%)*		*n = 3654 (25.0%)*		*n = 2536 (17.3%)*		*n = 1530 (10.5%)*		
	M	*CI95%*	*M*	*CI95%*	*M*	*CI95%*	*M*	*CI95%*	*M*	*CI95%*	
Depression Score (PHQ- 9)	3.5	[3.4; 3.6]	3.7	[3.6; 3.8]	4.1	[4.0;4.2]	4.6	[4.4;4.7]	5.0	[4.8;5.2]	<.0001[1)]
Anxiety Score (GAD-2)	0.7	[0.7; 0.7]	0.8	[.8; .8]	0.9	[0.9; 0.9]	1.0	[0.9; 1.0]	1.1	[1.0;1 .2]	<.0001[1)]
	%		%		%		%		%		
Depression (PHQ- 9 $\geq$10)	6.1		5.8		7.2		9.6		12.0		<.0001[2)]
Anxiety (GAD-2 $\geq$3)	4.5		5.4		6.5		8.0		10.0		<.0001[2)]
Depression (medical diagnosis)	10.1		10.7		11.2		14.2		14.8		<.0001[2)]
Anxiety (medical diagnosis)	6.3		6.0		7.2		8.3		9.9		<.0001[2)]

doi:10.1371/journal.pone.0155357.t001

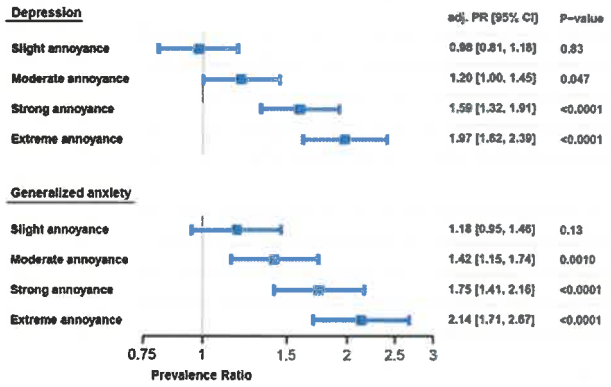

Fig 1. Association between noise annoyance, depression and anxiety. Note. Multiple generalized linear models with a binominal distribution and a log link function adjusted for sex, age and socioeconomic status were used.

doi:10.1371/journal.pone.0155357.g001

neighborhood outdoor (31.8%/ 1.2%), indoor (19.6%; 0.9%), railway (15.8%/0.7%) and industrial noise (19.6%/ 0.9%).

Fig 3 summarizes the sources of extreme noise annoyance. Clearly, aircraft noise has turned out the leading source with over 60%, followed by road traffic (18.1%), neighborhood (outdoor), industrial, neighborhood (indoor) and railway noise.

Discussion

The present study shows that the degree of noise annoyance reported by people living in the vicinity of the Frankfurt Airport and taking part in the Gutenberg Health Study (GHS) is strongly associated with the degree of depression and anxiety. Compared to other sources, annoyance by aircraft noise was prominent affecting almost 60% of the population and also accounted mostly for extreme degrees of annoyance. The vast majority of the large population-based sample reported noise annoyance; only 20.7% reported no annoyance. More than half (52.8%) of the population were at least moderately annoyed. Importantly, by adjusting for age, sex and socioeconomic status we could rule out possible demographic effects or effects of noisy low-socioeconomic environments.

When we looked at the sources of annoyance, the majority of participants reported annoyance due to aircraft, which exceeded all other sources of noise. Aircraft noise has also turned

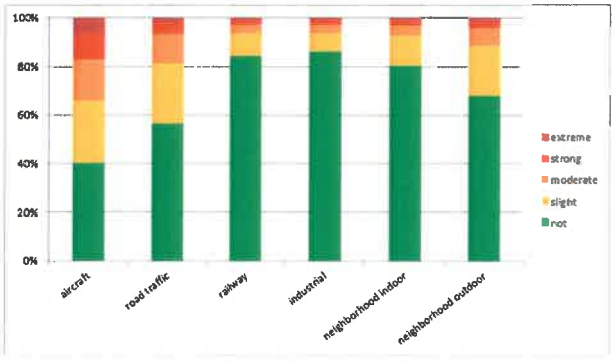

Fig 2. Degrees of overall annoyance according to different sources of noise.

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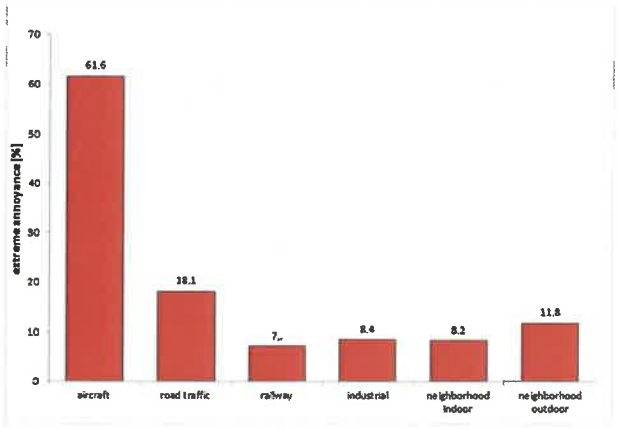

Fig 3. Sources of extreme annoyance (*N* = 1530).

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out as the leading source of extreme annoyance (with over 60%), followed by road traffic, neighborhood (outdoor), industrial, neighborhood (indoor) and railway noise. With respect to aircraft but not road traffic noise, there has been a substantial increase in annoyance reactions over the years at the same intensity of noise [5]. Babisch et al. recently demonstrated that annoyance ratings in the HYENA study were clearly higher than predicted by the EU standard curves [5].

Anxiety and depression belong to the most frequent and impairing conditions in the community; the 12-month prevalence of anxiety disorders was 14.0% and major depressive disorders afflicted 6.9% in Europe according to large epidemiological studies. Nearly one in four women and one in six men experience depression during their lifetime. Nearly twice the number of women reported anxiety disorders or depression compared to men. Living alone, a lower educational level, and a low socioeconomic status have been identified as risk factors for anxiety disorders and depression [10].

Occupational noise and depression have been studied most intensely, e.g. a large recent Korean survey by Yoon et al. [22] found that occupational noise annoyance was strongly associated to depressive symptoms and suicidal ideation in men and women (odds ratios OR 1.41 to 1.76). An Egyptian study of airport workers found hearing impairment, raised blood pressure, headaches, disturbed sleep, and symptoms of anxiety were more prominent among the noise exposed workers than the controls [23].

Findings regarding traffic noise, depression and anxiety are rather limited and somewhat controversial. In one study the association between traffic noise and depression was due to the link between noisy, low-socio-demographic environments and mental health [24]; other studies [6, 12, 13] found that the association between noise and mental symptoms was mediated by annoyance, respectively noise sensitivity [7]. A large, recent Danish study by Roswall et al. found that calculated residential exposure to road traffic and railway noise had significant, but small negative effects on quality of life [25].

Regarding aircraft noise, indirect evidence for a potential negative effect on mental health, respectively sleep was provided by Floud et al. [26] Aircraft noise during the day (OR = 1.28) and the night (OR = 1.27) was significantly associated with the intake of anxiolytics; the effects for annoyance were considerably stronger (OR = 1.78; OR = 1.77) [26]. The intake of antidepressants was only increased by noise annoyance at night (OR = 1.59) [26]. Based on health insurance data, the large case control study [27] found an increased likelihood of inpatient

treatment for depression in women (neither for men nor anxiety disorders) exposed to intensive night time aircraft noise; the same applied to the intake of antidepressants. A small case control study by Hardoy et al. [28] showed an increased risk for long-lasting syndromal anxiety states (Generalized Anxiety Disorder and Anxiety Disorder NOS) in participants exposed to aircraft noise.

As in the international literature, substantial proportions of the population were afflicted with depression (6.6%) and anxiety disorders (7.3%). Previous medical diagnoses of depression were reported by a total of 12.0%; medical diagnoses of anxiety disorder by 7.3%. According to our findings, the intensity of depression and anxiety, and also the proportions of medical diagnoses of depression, respectively anxiety increased with noise annoyance.

Importantly, the magnitude of the association between noise and depression/anxiety was comparable to the previously reported association of depression with coronary heart disease [2, 29–31]. Thus, in addition to direct negative cardiovascular effects of noise [2, 29–31] it is tempting to speculate there might be some indirect adverse effect of noise in inducing cardiovascular disease via causing depression and anxiety disorders.

More than half (52.8%) of the population were at least moderately annoyed and thus at an increased risk for depression and for generalized anxiety; the intensity of the risk increased steadily with the degree of annoyance amounting to a more than two-fold risk (2.12 for depression, 2.28 for generalized anxiety) at the level of extreme annoyance.

The demonstration of an association of noise annoyance with current depression and anxiety disorder is compatible with the hypothesis that annoyance induces stress, which in turn may precipitate or even worsen already existing depression and anxiety disorders. However, given the cross-sectional nature of our study and previous findings [6, 12, 13] we cannot preclude that depression, respectively anxiety disorders may also indicate a heightened noise sensitivity. Thus, existing mental disease may deteriorate due to noise [7]. As anxiety and depression are among the most frequent and burdening diseases in the general population, substantial parts of the population may thus be particularly vulnerable to environmental noise. Alternatively, increased annoyance may be a symptom of depression and anxiety related to the increased irritability sometimes found in these conditions or to the negativity to one's surroundings found in depression.

Strengths of our study are the large sample size of over 15.000 residents and the representative nature of the sample. While previous surveys usually assessed one or two kinds of noise (e.g. road, air traffic or occupational), we were able to cover a broad range of sources including neighborhood noise indoors and outdoors, and we were able to adjust for socio economic status. Limitations of the study refer to the age range (35 to 74 years) and the participation rate. Noise annoyance may be lower in younger people [7]. Further analyses will help to specify the contributions of specific sources of noise to annoyance during the day and in the sleep. The focus of this paper was on subjective annoyance, and we could not relate it to objective measures of noise exposition. Based on the cross-sectional nature of our data we cannot make causal statements on the relationship of annoyance to mental health, i.e. participants with mental health problems may be more noise sensitive and report higher annoyance [7]. We expect further clarification of these issues from our regular follow-up assessments of the 15,000 included cohort subjects in order to address the issue of causal relationships between annoyance and mental health.

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Author Contributions

Conceived and designed the experiments: MEB CJ PW KL MB HB MM JW EB TM. Performed the experiments: MEB PW KL MB TM. Analyzed the data: CJ MEB EMK. Contributed reagents/materials/analysis tools: MEB CJ EMK PW KL MB HB MM JW EB TM. Wrote the paper: MEB CJ EMK PW KL MB HB MM JW EB TM.

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EXHIBIT H

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 71, NO. 6, 2018

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.

ABBREVIATIONS AND ACRONYMS

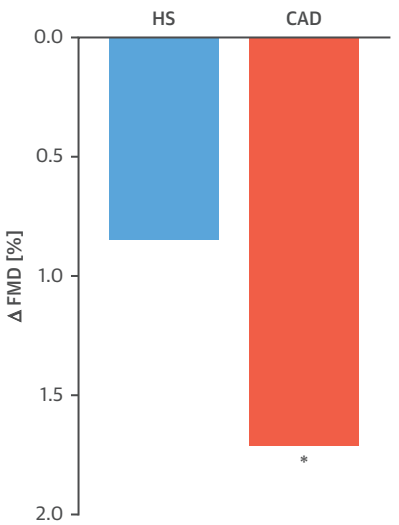
CVD = cardiovascular disease

eNOS = endothelial nitric oxide synthase

ADVERSE CARDIOVASCULAR EFFECTS OF NOISE IN HUMANS

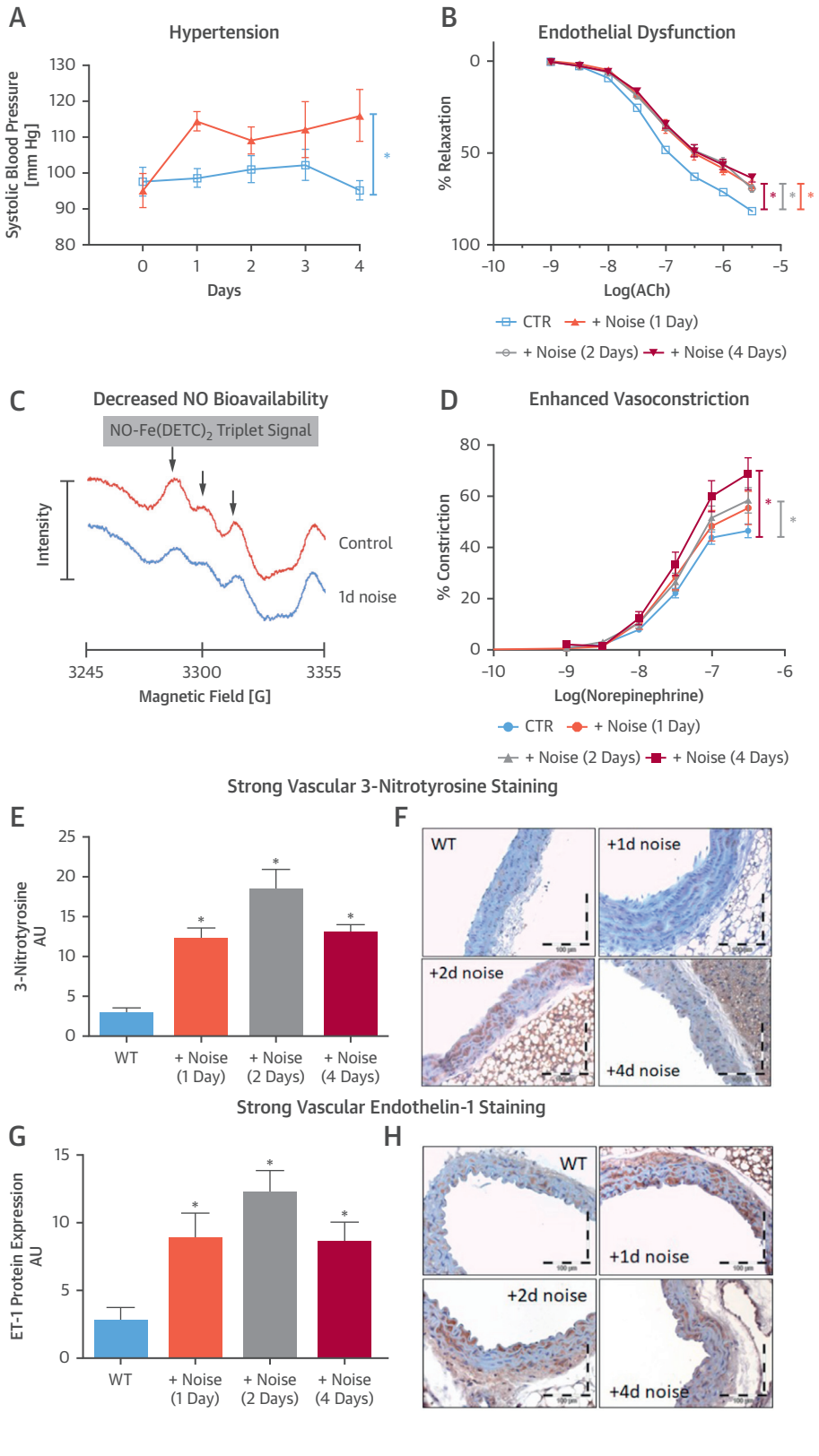
Translational studies addressing associations between noise and vascular (endothelial) function are rare. In a recent field study, we found that simulated nocturnal aircraft noise was associated with endothelial dysfunction and decreased sleep quality (14). Importantly, endothelial dysfunction was markedly 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

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



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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-1β, 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

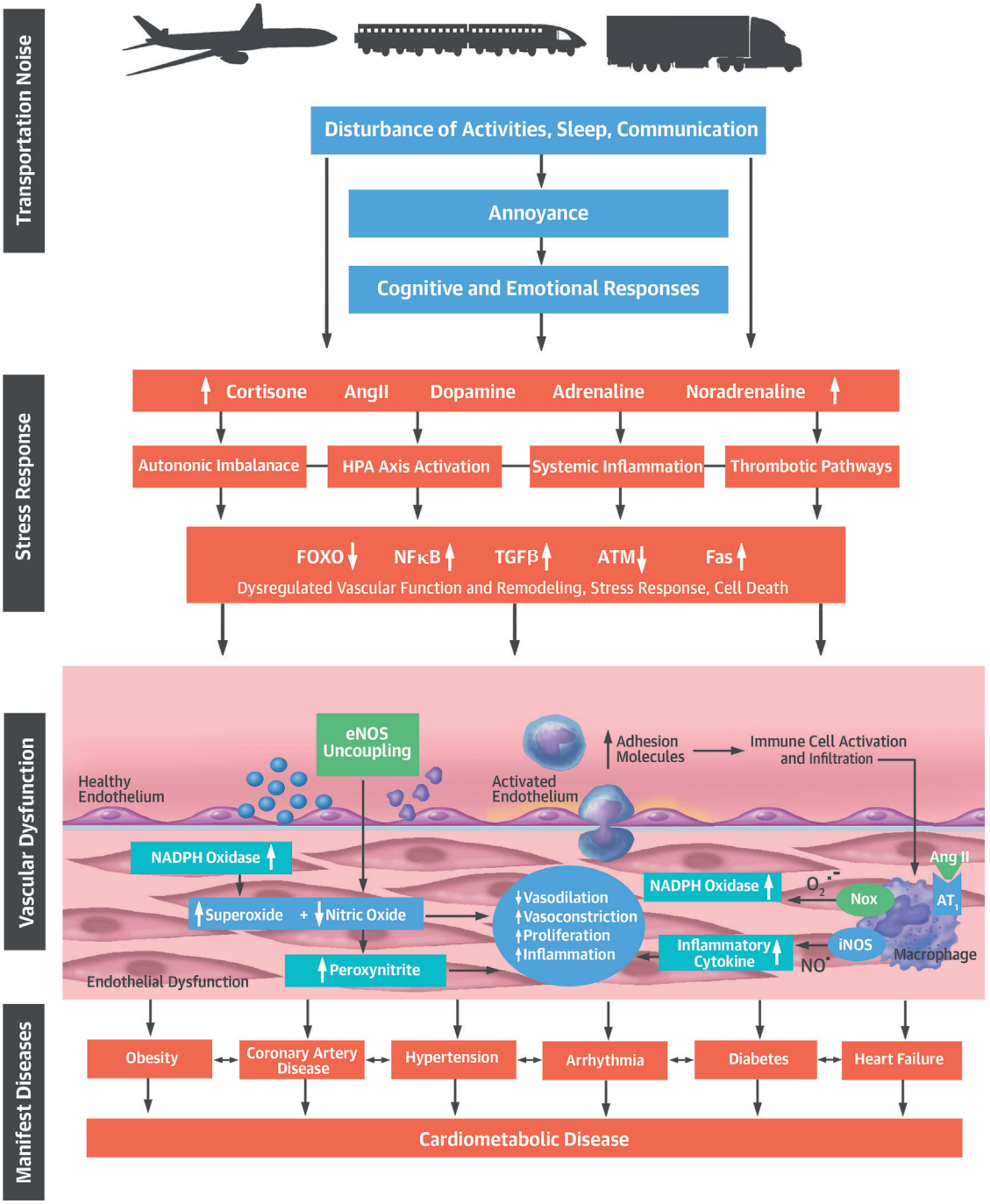
The quantity of epidemiological papers on traffic noise and CVD is rapidly growing, especially in recent years. At the same time, the research quality has increased considerably, with much larger study populations and increased focus on adjustment for air pollution. This has resulted in further evidence 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**



Münzel, T. et al. J Am Coll Cardiol. 2018;71(6):688–97.

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; AT_1 = 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; O_2 = oxygen; TGF = transforming growth factor.

FIGURE 3 Environmental Sources of Noise and Respective Sound Pressure Levels

Adapted from Münzel et al. (3) with permission of the publisher. Copyright © 2017, Oxford University Press. WHO = World Health Organization.

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-β1, and nuclear factor-κB, 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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