Acute cardiovascular mortality in communities surrounding an international airport: triggering effects of aircraft noise, temperature, and air pollution

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Prof. Dr. Marcel Mayor
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Summary

Environmental risk factors and cardiovascular diseases are among the leading causes of the global burden of disease. While the importance of transportation noise on health is being increasingly recognized, evidence is still lacking on the role of aircraft noise on cardiovascular health outcomes. In addition, it remains unclear whether aircraft noise can also act as a trigger of cardiovascular deaths, as observed for other environmental exposures such as air pollution.

The overall aim of this thesis was to investigate the role of night-time aircraft noise on acute cardiovascular mortality. Individual exposure to aircraft noise, air pollution, and temperature was calculated at home location with high spatial and temporal precision for 24,886 cases of cardiovascular deaths from the Swiss National Cohort occurring in the vicinity of Zurich airport between 2000 and 2015. This 'case only' study enabled the investigation of aircraft noise as a trigger of cause-specific cardiovascular mortality with minimum bias. The creation of an individual aircraft noise exposure assessment approach and precise nationwide air pollution models allowed the exploration of the individual and combined effects of extreme temperature and air pollution on acute fatal cardiovascular events.

This thesis provides the first evidence of the association between night-time aircraft noise exposure and acute cardiovascular mortality and highlights the importance of undisturbed, quiet nights. Since low average night-time noise levels may mask few loud events, it is essential that future noise guidelines integrate aircraft noise characteristics by using adequate exposure metrics with regards to cardiovascular health outcomes and by promoting the generalization of source-specific regulatory limits. Besides, comparing the risks of cause-specific cardiovascular mortality across several environmental exposures suggested independent triggering effects of aircraft noise, temperature, and air pollution. The association between acute cardiovascular mortality and particulate matter was confounded by nitrogen oxide, highlighting possible singularities in air pollutant mixtures in this particular setting located near a major airport. Finally, differences were observed in exposure levels and susceptibility across the different exposures and health outcomes, which are likely to take root in housing, physiological, social, and behavioural mechanisms.

Air travel will continue to be an important driver of development and economic growth. The results presented in this thesis underline the importance to address the public health impacts of aircraft noise at a policy-level and set the foundations to refine future aircraft noise regulations. In the context of a rapidly changing climate, public health and mitigation measures should be integrated in a comprehensive approach to improve environmental health as a whole and to promote sustainable, healthy, and equitable communities.

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List of Abbreviations

CI	Confidence Intervals;
CVD	Cardiovascular diseases;
DALY	Disability-adjusted life year;
dB	Decibel. Logarithmic scale to measure sound pressure levels;
EEA	European Environmental Agency;
ICAO	International Civial Aviation Organization;
ICD-10	International classification of disease, 10^{th} revision;
IR	Intermittency Ratio;
L_{AE}	A-weighted total energy of an event condensed on one second [dB];
L_{Aeq}	A-weighted equivalent continuous sound pressure level over a defined period of time [dB];
L_{Amax}	A-weighted maximum reached energy level of an event [dB];
L_{day}	Equivalent continuous sound pressure level when the reference time interval is the day (07:00 to 23:00) [dB];
L_{den}	Day-evening-night-weighted sound pressure level [dB], where evening levels get a 5 dB and night a 10 dB penalty;
L_{eq}	Equivalent continuous sound pressure level over a defined period of time [dB];
L_{max}	Maximum reached energy level of an event [dB];
L_{night}	Equivalent continuous sound pressure level when the reference time interval is the night (23:00 to 07:00) [dB];
NAO	Noise Abatement Ordinance from 15. December 1986;
NAT_{55}	Number of events with L_{Amax} exceeding a threshold of 55 dB;
NO_2	Nitrogen dioxide;
OR	Odds Ratio;
$PM_{2.5}$	Particular matter smaller or equal to 2.5μm;
SNC	Swiss National Cohort;
UFP	Ultra fine particles;
WHO	World Health Organization;
ZFI	Zürich Aircraft Noise Index;
ZRH	Zürich Airport.

Part I

Introduction

Chapter 1

Background

1.1 The environment and cardiovascular diseases: a major public health challenge

Environmental hazards are one of the greatest emerging threats to public health. According to the World Health Organization (WHO), about 12.6 million deaths globally (24% of all deaths) could be attributed to the environment, defined as 'all the physical, chemical and biological factors external to a person, and all related behaviours' [World Health Organization 2021]. From these 12.6 million, it was estimated that around two thirds (ca. 8.2 million deaths) originated of non-communicable diseases, number that could substantially be reduced by limiting their modifiable environmental risk factors [Prüss-Ustün et al. 2016]. Cardiovascular diseases (CVDs) cover a range of health disorders of the heart and blood vessels, including coronary heart diseases and cerebrovascular diseases. In 2017, they contributed to 17.8 million deaths and 35.6 million DALYs worldwide, making it the leading cause of death globally [Kyu et al. 2018]. CVDs also represent the largest contribution to the environmental burden of disease worldwide (Figure 1.1).

Currently, the burden of CVD is highest in low and middle-income countries. This situation is mostly the result of extensive prevention efforts made over the last decade, that resulted in the amelioration of several lifestyle factors (e.g. smoking, physical activity, etc.) and decline in the age-standardized CVD mortality in high-income countries [Roth et al. 2017].

Nonetheless, the epidemiological transition occurring in low and middle-income countries further contributes to moving the burden of diseases from infectious diseases towards non-communicable diseases [Yusuf et al. 2001]. In addition, with increasing urbanization and the overall ageing of the population worldwide, mortality and morbidity related to CVD are expected to rise alongside social and spatial disparities [Roth et al. 2015; Fairburn et al. 2019]. In Switzerland, chronic diseases, and especially car-

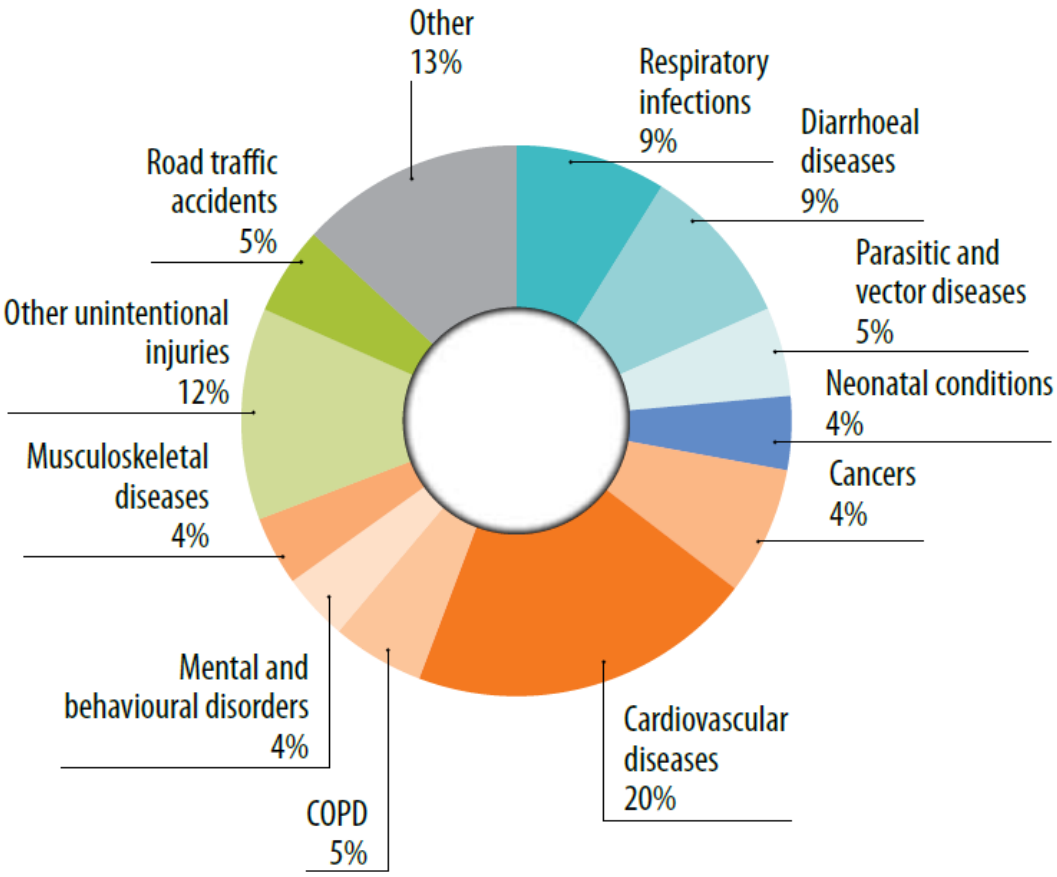

Figure 1.1: Main diseases contributing to the environmental burden of disease, all ages, world, 2012. Cardiovascular diseases contribute to 20% of the global environmental burden of disease.[1]

diovascular diseases, also play a major contribution on mortality and morbidity [Federal Statistical Office 2019]. It is essential to prevent the further increase in CVD by reducing its preventable risk factors.

Cardiovascular risk factors can be classified into three categories: (a) physiological (e.g. diabetes, hyperlipidaemia); (b) behavioural (e.g. smoking, alcohol consumption, physical inactivity); and (c) socioeconomic and environmental (e.g. noise, air pollution, sanitation, education) [Tzoulaki et al. 2016]. While some risk factors remain unmodifiable

[1]Figure reprinted with permission from "Preventing disease through healthy environments: a global assessment of the burden of disease from environmental risks". Prüss-Üstün, Annette, Wolf, J., Corvalán, Carlos F., Bos, R. Neira, Maria Purificación. World Health Organization. Copyright (2016). `https://apps.who.int/iris/handle/10665/204585`. Accessed on 21.12.2021.

(e.g. genetic background), most of them are influenced by a combination of behavioural and environmental risk factors. Besides, behaviour are often modified by geographical and environmental conditions. Therefore, improvements in environmental and living conditions can benefit both environmental and behavioural risk factors [Bhatnagar 2017].

Since it has been shown that a reduction in environmental pollution can effectively reduce mortality from coronary heart diseases [Bhatnagar 2017], it is crucial to promote environmental health to prevent the further increase in CVDs worldwide. While the individual cardiovascular risk increase associated with environmental exposures is generally limited, their contribution to public health is particularly relevant, simply because a large portion of the population is exposed. However, while environmental noise is an important contributor to cardiovascular mortality, it is not systematically addressed in population risk calculations and health policies [Nawrot et al. 2011; European Environment Agency 2020]. The focus of this thesis is to contribute to the growing body of evidence on the cardiovascular health impact of aircraft noise.

1.2 What is noise?

Noise is defined as an unwanted or harmful sound [European Commission 2002]. Noise from road, railways and aircraft, covered under the term 'transportation noise' are major contributors of environmental noise. Unlike other environmental exposures (e.g air pollution, high temperatures), noise can vary rapidly over time, which makes it particularly difficult to capture and characterize.

Noise or sound is created by a mechanical wave conducted through air, from the emitting source to the receiver's ear. A sound can be characterized by the following elements: (a) the frequency (or perceived as high or low); (b) the intensity (loudness); (c) the spectrum (composition of the sound in terms of frequencies, that makes its tone recognizable from another sound); and (d) its evolution over time. The human ear can perceive sounds frequencies ranging from 20 to 20'000 Hz. Most epidemiological studies investigating the health effects of environmental noise focus on noise intensity, measured on a logarithmic scale, the decibel scale (Figure 1.2). The most commonly used metrics are L_{eq} (equivalent continuous sound pressure level) and L_{Aeq}, its A-weighted counterpart, corrected for the human audition at different frequencies. L_{eq} represents the overall sound energy of an event averaged over its duration and gives an indication of the mean level of sound pressure level over a given period of time (Figure 1.3).

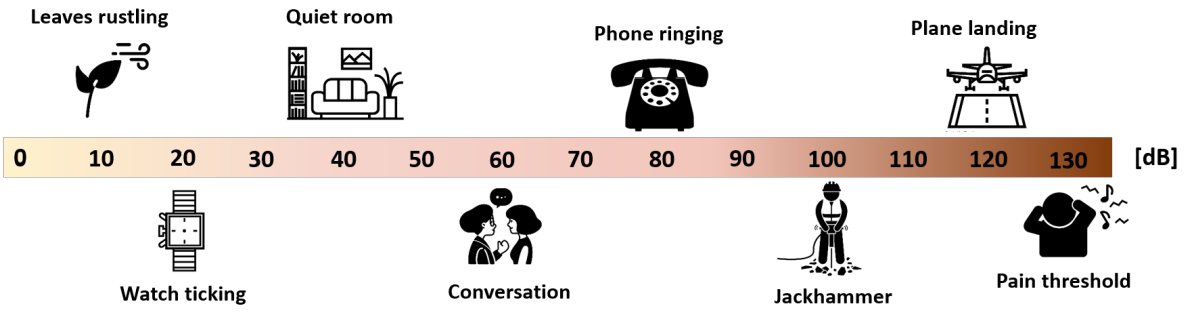

Figure 1.2: The decibel scale in the human hearing range. The hearing threshold is set at 0 dB. Typically, a quiet conversation lies around 60 dB, and a plane landing around 120 dB. The pain threshold lies around 130 dB.

Two other frequently used noise metrics are L_{max} (maximum sound pressure level) and L_{den}, measuring the day - evening - night weighted sound pressure level, where evening levels get a 5 dB and night a 10 dB penalty. L_{den} is particularly useful in studies investigating long-term effects of noise on health, as it compensates for the fact that traffic noise may be more relevant or audible during the more quiet times and during sleeping phases [World Health Organization 2018b]. However, L_{eq} and L_{den} do not capture rapid variations of the noise intensity over time. For individual sources with high temporal variation such as aircraft and railway noise, other metrics can account for individual noise events such as the number above threshold (NAT), as presented in Figure 1.3.

Noise characteristics, such as evolution over time, tone, frequency, but also subjective perception, may affect the human response to environmental noise, as reflected in different health outcomes associated with different noise sources. For instance, aircraft noise usually causes higher annoyance levels than road and railway noise [Münzel et al. 2020a]. Furthermore, it seems that annoyance to aircraft noise is greater than can be explained by the changes in average noise levels [Brown and Kamp 2017]. To this day, it is still unclear which characteristics of aircraft noise can explain this difference in annoyance compared to other noise sources, and which exposure metrics are best suited to capture this difference [Haubrich et al. 2019]. Identifying and accounting for individual noise characteristics is particularly important to accurately measure the individual exposure levels and their associated health outcomes.

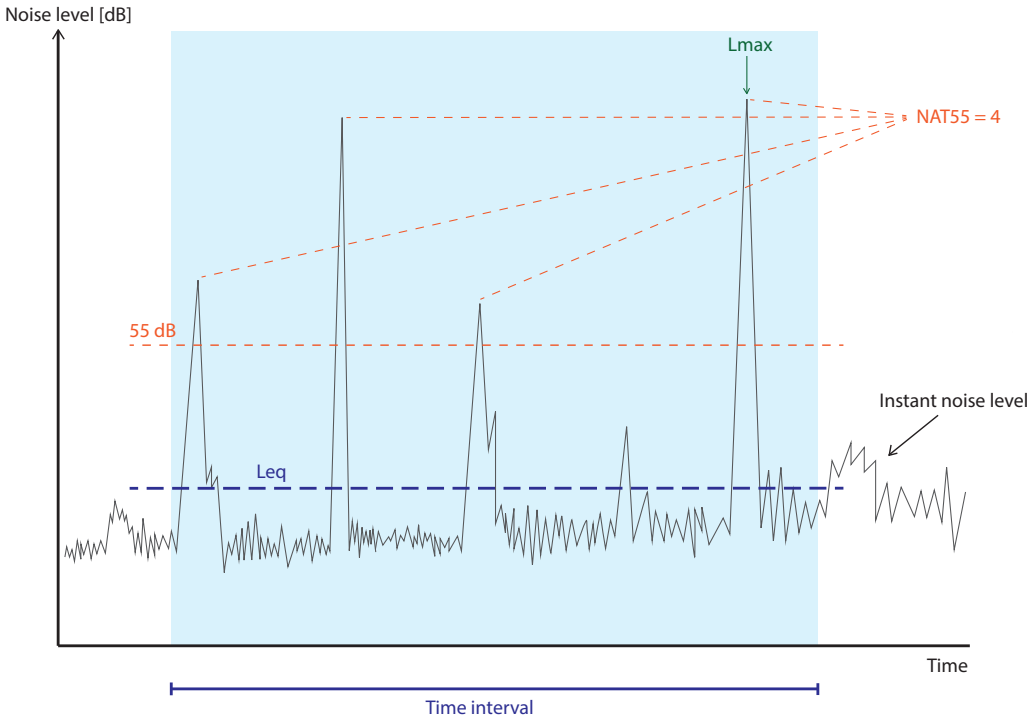

Figure 1.3: Overview of L_{eq}, L_{max} and NAT_{55} for a given time window in relation to instant noise level.

1.3 Noise and health: from scientific evidence to public health measures

1.3.1 The burden of environmental noise

Environmental noise is considered to be the second most important environmental contributor to the burden of disease in Europe, following fine particulate matter [Hänninen et al. 2014]. Apart from the auditory effects of high noise levels, such as hearing loss and tinnitus, environmental noise can affect health in various ways. Long-term exposure to environmental noise is known to cause adverse cardiorespiratory health outcomes [Van Kempen et al. 2018], annoyance [Brown and Kamp 2017], cognitive impairment among children [Foraster et al. 2019], and to affect well-being [Héritier et al. 2014], endothelial function [Herzog et al. 2019], and metabolic functions [Thiesse et al. 2018; Vienneau

et al. 2019]. Long-term exposure to environmental noise contributes of 12'000 premature deaths and 48'000 new cases of ischaemic heart diseases, and 1 million of healthy years life lost in Europe each year (61,000 for ischemic heart disease, 903,000 for sleep disturbance, and 654,000 years for annoyance) [European Environment Agency 2020; World Health Organization 2011].

Overall, it is estimated that about 113 million Europeans are exposed to long-term traffic noise levels of at least 55dB(A) L_{den} from which 4 million are exposed to high levels of aircraft noise [European Environment Agency 2020]. In Switzerland, about 65'000 persons are exposed to air traffic noise excessing the imission limit values during the day and 95'000 during the night [Swiss Confederation 2017], a large part which are located in urban or peri-urban areas [Federal Office for the Environment 2019]. According to the International Civil Aviation Organization (ICAO), passenger air traffic increased by 6% in 2014 and by 6.7% in 2015 [ICAO 2020]. With always more people living in cities and increasing mobility, the proportion of population exposed to potentially harmful levels of transportation noise is expected to rise in future years [European Environment Agency 2020].

1.3.2 From the ear to the heart

While the exact pathways that link environmental noise to cardiovascular diseases and mortality are not fully understood, there seems to be a clear implication of cortical activation, sleep disturbance, oxidative stress, and sympathetic response that can lead to mortality. To better understand how a sound — perceived through the ear — can affect biological and physiological reactions, one needs to turn to the basic concepts of stress and stress response [Münzel et al. 2018]. Just like sight, the sense of hearing takes its primarily function in serving the organism to perceive and react to its direct environment, enabling it to respond to an immediate danger. As formulated by Henry and Stephens [Henry and Stephens 2013], the two possible reactions to a stress situation are (1) 'fight or flight', characterized by the immediate activation of a sympathetic response; and (2) 'freeze', characterized by the liberation of stress hormones (corticosteroids). Both reactions are susceptible to induce short and long-term physiological and metabolic changes, with possible consequences on the cardiovascular system.

The idea that noise might have non-auditory effects and affect human life and health is not new; in 1910, Robert Koch already warned of the public health burden of noise

that humans will face in the future, which he compared to infectious scourges of his time, such as pest and cholera. The currently most widespread and accepted theory on the pathways in which noise affects cardiovascular health have been first described by [Babisch et al. 2014] and makes a distinction between a direct pathway mediated by sleep and an indirect pathway involving a cognitive and emotional reaction to noise (Figure 1.4). Both pathways eventually impact cardiovascular risk factors (hormonal, physiological and behavioural), can increase blood pressure and viscosity, which can eventually lead to hypertension, ischaemic heart diseases, and death [Münzel et al. 2020a].

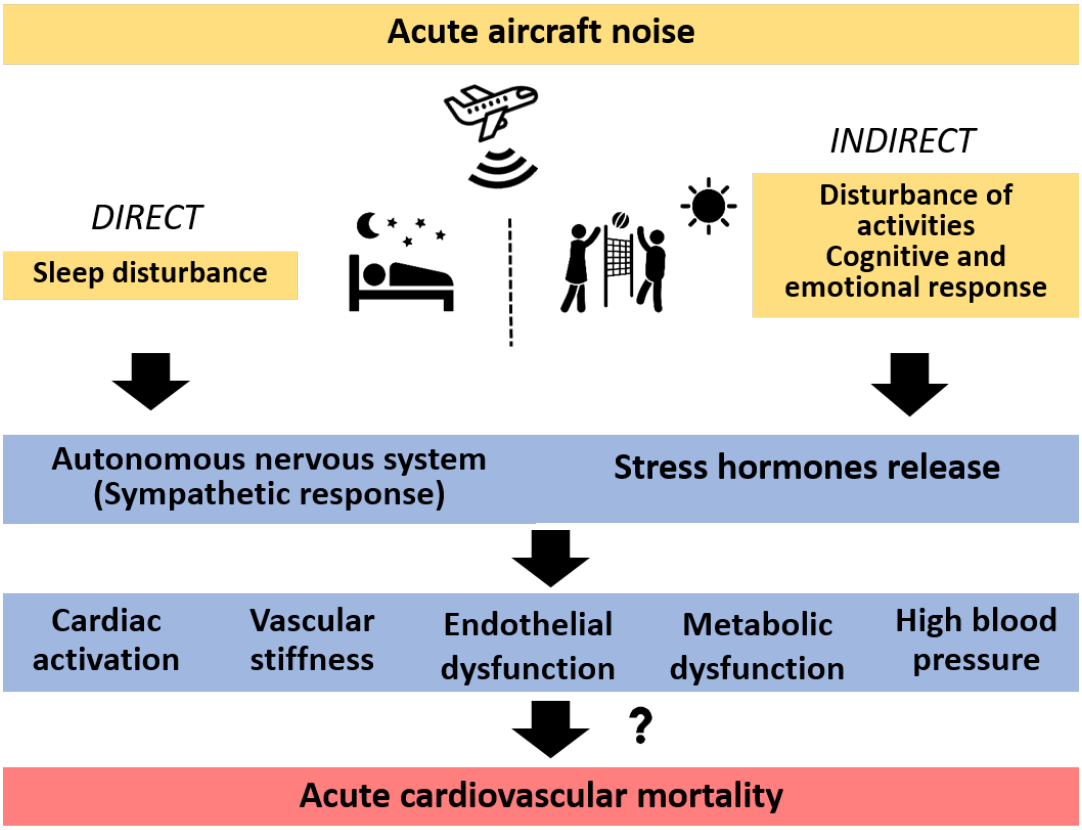

Figure 1.4: Noise reaction scheme explaining the acute response to aircraft noise exposure. The link between the physiological response (in blue) and acute cardiovascular mortality (in red) is not established yet.

To inform the new WHO environmental noise guidelines, meta-analyses were conducted on all existing evidence of the association between environmental noise and cardiovascular diseases published until 2015 [World Health Organization 2018b]. It was estimated that the risk of ischaemic heart diseases increased by 8% (risk ratio (RR) = 1.08 [1.01–1.15]) per 10dB increase in road traffic noise [Van Kempen et al. 2018]. For

aircraft noise, results were generally less consistent and mainly based on cross-sectional studies. Most recent evidence however reports an increase of incidence of ischaemic heart diseases (RR = 1.03 [0.98–1.09]) and diabetes (RR = 1.20 [0.88–1.63]) per 10 dB increase in aircraft noise [Vienneau et al. 2019]. Compared to other sources of traffic noise, aircraft noise seems to be the one affecting annoyance the most [Haubrich et al. 2019; Brink et al. 2019]. Annoyance related to aircraft noise is relevant in terms of general well-being and quality of life, but also, it is suspected to modify the association between noise exposure and the risk of hypertension [Babisch et al. 2013] and to alter behavioural risk factors of cardiovascular diseases, such as physical activity [Foraster et al. 2016]. Yet, further research based on longitudinal data is required to generate increased evidence on the cardiovascular health outcomes associated with aircraft noise [Van Kempen et al. 2018], including a better understanding of their exposure-response relationship [Vienneau et al. 2015].

1.3.3 Just let me sleep!

Night-time noise exposure is believed to be of particular importance in the development of cardiovascular diseases, mainly through noise-induced sleep disruption [Münzel et al. 2014; Sayk et al. 2007]. Experimental studies have shown that sleep disruption acts similarly on the human physiology than perturbation of the circadian rhythm and induces inflammatory responses [Qin and Deng 2015; Cappuccio et al. 2011]. Night-time noise exposure is also associated with increased brain activity and cardiac activation [Basner et al. 2008], deteriorated sleep quality [Kröller-Schön et al. 2018; Röösli et al. 2019], insulin tolerance [Thiesse et al. 2018], vascular stiffness [Foraster et al. 2017], and endothelial dysfunction [Schmidt et al. 2013], mediated through the vascular production of reactive oxygen species [Münzel et al. 2020a]. Herzog and colleagues recently showed that night-time exposure to railway noise not only affected sleep quality, but also endothelial function and induced pre-coagulation responses in healthy subjects [Herzog et al. 2019]. This work is particularly relevant, as it presents a clear link between sleep disruption and acute changes in protein and gene expression. Thanks to a recent randomized trial, the causality of the association between night-time aircraft noise and impairment of vascular and endothelial functions is now established with quasi-certainty [Schmidt et al. 2020]. In this study, vascular function was similarly affected by both low and high events numbers (for a similar L_{eq}) but more events were associated with worse outcomes on the cardiac function. While the particular importance of nighttime exposure has been established in relation to different physiological responses to traffic noise, further research is

needed to establish the specific relevance of different night-time noise timings in relation to cardiovascular health [Héritier et al. 2018].

1.3.4 Aircraft noise and acute cardiovascular mortality

Why aircraft noise?

Recent evidence shows that loud events and intermittent sounds may have more detrimental effects on sleep and associated cardiovascular diseases than continuous noise sources [Seidler et al. 2018; Münzel et al. 2020a; Schmidt et al. 2020]. Aircraft noise is a particular exposure, as it is subject to higher temporal variations than other noise sources (see Section 1.2). Unlike road or railway noise, aircraft noise can be mainly controlled at its source. Except for houses with improved sound insulation, the equivalent of sound barriers typically used to protect from railway and road traffic noise do not exist to limit noise from air traffic. Despite an estimated insufficient level of evidence available to conclude to a causal relationship between aircraft noise exposure and the risk of cardiovascular diseases in context of the WHO environmental noise guidelines [World Health Organization 2018b], many studies have been published that supported the implication of aircraft noise in various physiological changes (e.g. metabolic disorders, endothelial dysfunction, and high blood pressure) [Thiesse et al. 2018; Schmidt et al. 2013; Herzog et al. 2019]. Aircraft noise has also been reported to be associated with increased risk of hypertension [Dimakopoulou et al. 2017] and stroke [Weihofen et al. 2019]. However, the direct link between night-time aircraft noise and acute cardiovascular mortality has not been established yet (Figure 1.4), which is the focus of this PhD thesis.

Long-term versus acute health effects

Given its implication in short-term physiological changes such as high blood pressure or vascular function, it is likely that night-time aircraft noise may also trigger acute cardiovascular mortality. In addition, several environmental exposures have been shown to induce acute mortality within days or even hours. In 2011, Nawrot and colleagues have published a review of exposures (both behavioural and environmental) known to trigger myocardial infarction and have conducted a comparative risk assessment, reporting increased risk of acute myocardial infarction associated with alcohol drinking, stress, anger, physical exercise, drug use, or even coffee intake [Nawrot et al. 2011]. Compared to behavioural risk factors, such as drug use or physical exercise, environmental expo-

sure to air pollution carried lower individual risk estimates but was responsible of a large number of excess deaths in the population. Due to its wide distribution, it represents an important target for public health interventions. Aircraft noise could present a similar trend if its role as a trigger of cardiovascular events was to be proven.

1.3.5 Further triggers of cardiovascular mortality

Other environmental exposures are also susceptible to trigger acute cardiovascular mortality and may therefore confound the association between aircraft noise and acute cardiovascular mortality. It is for instance the case of air pollution and extreme temperature [Arbuthnott et al. 2020; Achilleos et al. 2017], which need to be considered in this research, as described below.

Extreme temperature

The physiological response to heat is a common adaptive process for healthy individuals, including perspiration, vasodilatation, and increased heart rate. In contrast, cold temperature induces a generalized vasoconstriction to regulate the body temperature. Both warm and cold extreme temperature can increase the risk of cardiovascular mortality, due to a reduced blood supply to different organs in the case of heat, or to an excessive stress on the heart muscle due to increased resistance through cold-induced vasoconstriction [Crandall and Wilson 2011]. A comparative study between countries showed that the optimum temperature (lowest all-cause mortality), thresholds and shape of the association between temperature and mortality varied between climates and countries worldwide [Gasparrini et al. 2015]. In Switzerland, increasingly frequent heatwaves have become an important cause of acute mortality, where maximum temperatures above the median in the summer months were associated with an increased mortality (RR=1.15 [1.08–1.22]). This was especially evident in the beginning of the summer, before people could begin to adapt to heat over the summer months [Ragettli et al. 2017]. Public health measures and mitigation plans can help reduce mortality related to heat events, as adopted in Switzerland after 2003 [Vicedo-Cabrera et al. 2016]. For instance, cantons with extensive prevention plans reported positive health benefits, especially during the summers 2018 and 2019 [Ragettli and Röösli 2021]. Strengthening the existing mitigation plans and extending them to the national level is critical to reduce future excess mortality.

Air pollution

Acute exposure to air pollution such as particulate matter can also lead to cardiovascular diseases, typically observed within 24 to 48h after exposure [Nawrot et al. 2011; Buteau et al. 2018]. Air pollutants such as particulate matter of various size fractions (e.g. $PM_{2.5}$, PM_{10}), and nitrogen dioxide (NO_2) can cause inflammation of the airways, high blood pressure, and increased blood coagulability. These physiological reactions lead to an increase in both long and short-term risks of ischaemic heart diseases and mortality [Achilleos et al. 2017; Faustini, Rapp, and Forastiere 2014]. Based on their size, fine particles may cause different health outcomes. For instance, PM_{10} usually deposit in the larger or middle airways and cause local inflammation, which can lead to increased susceptibility to airways infections. Smaller particles like $PM_{2.5}$ and ultra-fine particles (UFP) can penetrate much deeper and cross the alveolar-capillary barrier. UFP has the ability to travel to most organs through the blood stream and can cause local toxicity. When deposited on the endothelial layers, UFP increase plaque instability and the potential liberation of thrombi [Du et al. 2016]. NO_2 is a gaseous air pollutant resulting in large part from road traffic and industry. In the bloodstream, it leads to inflammation — mainly through reactive oxygen species — and can cause the formation of blood clots that in turn can obstruct small arteries and lead to local ischaemia [Persinger et al. 2002]. Air pollution may also increase the heart rate and contractibility [Faustini, Rapp, and Forastiere 2014]. Both NO_2 and $PM_{2.5}$ annual mean concentration limits — set at 30 and 10 $\mu g/m^3$ respectively — are frequently exceeded in Switzerland, especially in urban settings and in proximity to roads [Swiss Confederation 2018].

In the context of a changing climate, both extreme temperature and extreme environmental conditions are expected to be more frequent. A deeper understanding of the individual and combined effects of weather, noise, and air pollution on cardiovascular mortality is important to predict future environmental health scenarios and to inform public health policies [Vicedo-Cabrera et al. 2018b].

1.3.6 Regulation and mitigation of environmental noise

In Europe

Over the past decades, research on the health effects of environmental noise has been rapidly increasing. The WHO recently published new guidelines for environmental

noise in the European region [World Health Organization 2018b], including systematic reviews gathering evidence on the effects of environmental noise on the cardiovascular system [Van Kempen et al. 2018]. For aircraft noise, it is recommended to reduce levels below 45 dB L_{den} and 40 dB L_{night}. It also recommended that governments and policies give priority to populated areas exposed to high levels of noise during the night, due to the evidence of harmful effects of aircraft noise on sleep [World Health Organization 2018b]. According to the European Environmental Agency (EEA), most European countries have set regulatory limits above those recommended by the WHO, especially in the case of aircraft noise, as most of them do not consider differential regulatory limits for aircraft noise as compared to other sources. However, adverse health outcomes are likely to occur even below the levels recommended by the new WHO environmental noise guidelines [European Environment Agency 2020].

In Switzerland

Environmental noise is regulated at the national level on the basis of the Noise Abatement Ordinance (NAO) of 1986 [Swiss Confederation 2019]. Currently, the regulatory limits for planning, emissions and alarm are set for different types of zoning and buildings. For residential areas, night-time limits for planning and alarm are 45 and 65 dB respectively, where specific measures are required, such as noise-insulated windows [Swiss Confederation 2019]. A national plan for noise mitigation was adopted in 2017 by the Swiss Federal Council, which sets the basis for reduction of noise emissions at sources and emphasizes the importance of noise consideration in future urban planning [Swiss Confederation 2017]. Since aircraft noise can mainly be limited at its source, most efforts are focussed on regulating air routes, air schedules, and promoting less noisy aircraft. This is also recommended by the International Civil Aviation Organization (ICAO), which promotes a balanced approach based on (1) reduction at source; (2) land use management; (3) optimization of flights profiles; and (4) flight restrictions. Zurich Airport was subject to a nighttime flight ban from 00:30 to 05:00 (approaches) and 06:00 (departures) in 2000, which was extended to 23:30 to 06:00 in 2010 [Zurich Airport 2021]. At the national level, air traffic is regulated through the Federal Act on Civil Aviation [Federal Office of Civil Aviation 2021]. The NAO requires all airports to calculate and report aircraft noise emission levels. At Zurich Airport, these calculations are performed by the Swiss Federal Laboratories for Materials Testing and Research (Empa).

Public health measures on environmental exposures that affect a large part of the population are critical for improving health and mitigating future healthcare costs. In Switzerland, it is estimated that about 12% of the country's annual gross domestic product is allocated to health [Federal Statistical Office 2018]. In 2017, health costs related to environmental noise reached 1'500 million CHF in Switzerland (e.g. health costs, loss of productivity). Overall, the external costs of transportation noise (including loss of property value) are estimated to 1.9 billion CHF yearly [Swiss Confederation 2017].

1.3.7 Environmental health equity

The burden of environmental exposures and their associated public health challenges is not equally distributed among the population [World Health Organization 2010]. In England, for example, NO_2 levels were significantly higher among the most financially deprived groups of the population [Fairburn et al. 2019]. With noise exposure, however, it is not clear which groups of the population are most vulnerable, in terms of both noise exposure levels and health responses [World Health Organization 2018b].

Social inequalities in noise and other environmental exposures are usually difficult to compare, due to the heterogeneity of the indicators used [Dreger et al. 2019]. Nevertheless, material indicators such as low income, poor living area, and lack of housing ownership seem to be consistently associated with increased exposure to traffic noise. High noise levels were almost never observed for the highest socio-economic groups [Dreger et al. 2019], whereas ethnic minorities tend to be excessively exposed to environmental noise, compared to the general population [Casey et al. 2017; Tonne et al. 2018]. Besides being increasingly exposed to outdoor environmental pollutants, some groups of the population also tend to live in older, less insulated buildings and present reduced coping capacities [European Environment Agency 2020]. In Germany, people with less than 13 years of education were found to be increasingly susceptible to depression in association with road traffic noise, compared to the rest of the population [Orban et al. 2016]. Furthermore, pregnant women, the elderly, and children could be at higher susceptibility to noise-related adverse health outcomes due to disrupted sleep patterns [European Environment Agency 2020].

When assessing health outcomes associated with environmental exposures, it is important to consider not only possible differential exposure levels, but also individual

susceptibility and capacity of response to these exposures, as these three dimensions taken together define the overall vulnerability of a person or a group of the population [Diderichsen, Hallqvist, and Whitehead 2019]. Currently, except for a particular focus on children's health, public health policies are still very limited in terms of protection of the most vulnerable to noise-related health outcomes. It is therefore critical to identify individual, social, and economical characteristics that affect vulnerability to noise and other environmental exposures in order to inform future health policies and reduce environmental health inequities.

1.4 Rationale

Noise pollution has gained public interest and visibility over the past couple of years. While the long-term effects of traffic noise on health are increasingly recognized, little is known about the possible role of aircraft noise on acute cardiovascular mortality. Despite the potential of aircraft noise to trigger acute physiological responses and growing evidence of the implication of sleep in the pathogenesis of diverse cardiovascular diseases, it remains to be proven if these short-term physiological responses to night-time aircraft noise also translate into acute cardiovascular mortality. Finally, current knowledge is limited towards the relevant timing, characteristics, and exposure-response relationship in the association between aircraft noise and cardiovascular mortality [Vienneau et al. 2015]. Evidence is also limited in terms of individual and social vulnerabilities to noise-related cardiovascular diseases.

Since air traffic is expected to increase in future years, increasing the current knowledge on the role of night-time aircraft noise exposure and timing on cardiovascular health outcomes is crucial to inform future public health policies and can help promoting cardiovascular health globally.

This PhD thesis has been especially designed to investigate the acute effects of aircraft noise. Based on a robust study design and precise individual exposure calculations, this thesis can contribute to a better understanding of the acute effects of night-time noise on cardiovascular mortality. The cause-specific and multiple exposures approach will further contribute to a deeper understanding of real-life exposure to environmental factors and their effect on the health of different groups of the population.

Chapter 2

Methodological approach

The work presented in this PhD thesis was conducted at the Swiss Tropical and Public Health Insitute (SwissTPH), in the Environmental Exposures and Health Unit, Epidemiology and Public Health Department and affiliated to the University of Basel. This research is part of the TraNQuIL (Transportation Noise: Quantitative Methods for Investigating Acute and Long Term Health Effects) project, a collaboration between Swiss TPH in Basel and the Swiss Federal Laboratories for Materials Science and Technology (Empa) in Dübendorf. The overall aim of the TraNQuIL project is to obtain a thorough understanding on how transportation noise affects human health. This PhD thesis specifically addresses the work package 1 entitled 'Case crossover study on the triggering effects of noise events on cardiovascular mortality'.

2.1 Aims and objectives

The overall aim of this thesis is to contribute to a better understanding of the role of aircraft noise in acute cardiovascular mortality. In order to address this research aim, the following specific objectives were identified:

Objective 1: To assess individual home exposure to nighttime aircraft noise for a case-crossover study population on case and control days, and specific nighttime exposure windows.

Objective 2: To model nationwide daily NO_2 levels at fine spatial resolution.

Objective 3: To describe and quantify the association between individual night-time aircraft noise levels and cause-specific acute cardiovascular mortality:

(a) To identify the most relevant exposure window for short-term and potential exposure-response threshold in the association between night-time aircraft noise and cardiovascular mortality;

(b) To identify and characterize the population most affected by short-term aircraft noise exposure.

Objective 4: To describe and quantify the association between extreme temperature and cause-specific acute cardiovascular mortality:

(a) To identify and characterize the population most affected by short-term warm and cold temperatures;

(b) To investigate possible interaction between temperature and air pollution for the association with cardiovascular mortality.

Objective 5: To investigate the role of air pollution on acute cardiovascular mortality:

(a) To assess the mutual contributions of NO_2, $PM_{2.5}$, temperature, and aircraft noise on the association with acute cardiovascular mortality;

(b) To identify and characterize the population most affected by NO_2 and $PM_{2.5}$ in relation to acute cardiovascular mortality.

2.2 Research concept and outline

Each of the above identified specific objectives corresponds to a chapter of this thesis. Part II, presents the exposure assessment procedure for this study (objectives 1 and 2). Part III, covers the results from the health outcomes analyses investigating the acute effects of nighttime aircraft noise, temperature, and air pollution on cardiovascular mortality (objectives 3, 4, and 5). All health outcomes analyses were based on the same study population and design, as described below.

2.2.1 Study population

The study population was selected from the Swiss National Cohort (SNC) [Spoerri et al. 2010] and includes all individuals aged more than 30 years, dying from a cardiovascular cause (ICD10 classification I00 to I99) between 2000 and 2015. The study area was limited to the vicinity of Zurich airport as potentially exposed to high levels of aircraft noise, identified using the Zurich Aircraft Noise Index perimeter for the highly annoyed and the highly sleep disturbed (minimum L_{Aeq} of 47 dB during the day and/or 37 dB during the night) [Schäffer et al. 2012] (Figure 2.1, part A). Geocoded residences at the time of death were available from the SNC, together with personal information such as cause and time of death and detailed socio-demographic and building characteristics.

2.2.2 Study design

This case-crossover study has been especially designed to investigate the acute effects of aircraft noise on mortality and is used throughout the different chapters of this thesis. This study design enables to (i) adjust for individual and external characteristics that are stable over short periods of time; (ii) make use individual environmental exposures with high spatial and temporal precision; and (iii) simplify the computations with use of conditional logistic regression, most individual characteristics being excluded from the regression analyses. In brief, each case of cardiovascular death was matched with up to four control events, selected on the same day of the week within the same month (Figure 2.1, part B). Similar to a case-control study analysis, odds ratio are calculated by comparing exposure levels between case and control events (Figure 2.1, part C) using conditional logistic regression. The choice of control events both before and after the day of death (time-stratified sampling approach) further reduces the risk of bias associated with temporal trends [Janes, Sheppard, and Lumley 2005; Lumley and Levy 2000]. The expression ? 'case and control events' are used throughout this thesis and is equivalent to 'case windows' and 'referent windows' sometimes used in similar studies [Janes, Sheppard, and Lumley 2005].

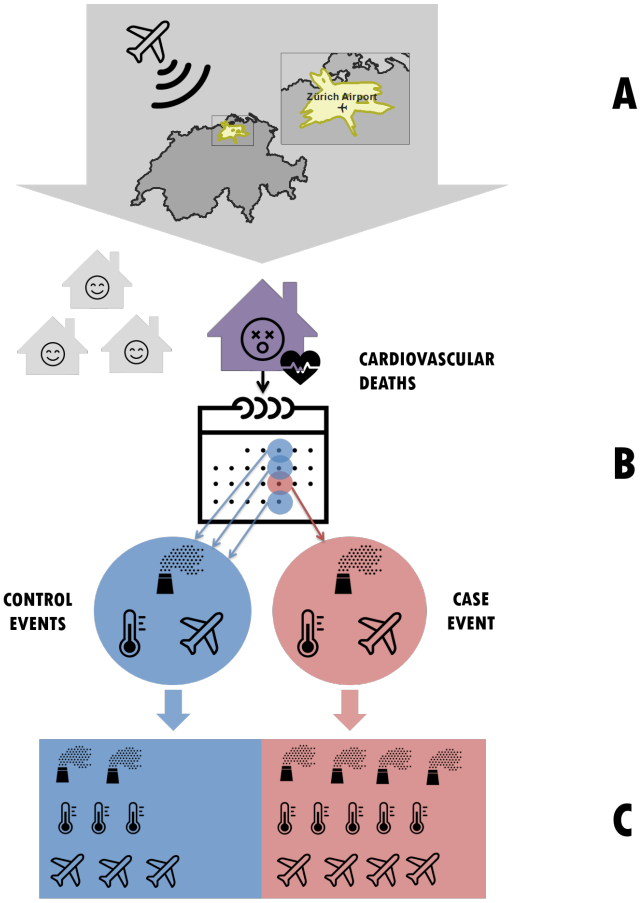

Figure 2.1: Overview of the methodological approach for this case-crossover study, including the choice of the study population around Zurich airport and used throughout this thesis (A), the selection of case and control events (B), and the comparison of the exposure levels between case and control events (C).

2.2.3 Part II: Exposure assessment

Objective 1: Individual Aircraft Noise Exposure Assessment for a Case-Crossover Study in Switzerland

With a main focus on nighttime aircraft noise, Chapter 3 presents a novel approach to assess individual aircraft noise exposure with high temporal and spatial resolution for the 24,886 identified cardiovascular deaths in our study population. The exposure windows of interest were defined as follows: (i) for deaths occurring during the day (23:00-07:00), we considered aircraft noise exposure 2 hours preceding the time of death; (ii) for deaths occurring during the day (07:00-23:00), we considered aircraft noise during several

exposure windows in the night preceding death: evening (19:00-23:00), early night (23:00-23:30), core night (23:30-06:00), early morning (06:00-07:00), overall night (23:00-07:00). Outdoor noise exposure at the home address was calculated for the described night-time exposure windows using detailed information of flight operations from Zurich Airport combined with noise footprints calculated for major aircraft types and air routes. The noise footprints have been calculated for Zurich Airport using flight trajectories obtained from radar data for each year, time of the day, aircraft type, and air route at 250 × 250 m resolution. We estimated three different noise metrics: mean sound pressure level (L_{Aeq}), maximum sound pressure level (L_{Amax}), and number above threshold 55 dB (NAT_{55}).

Objective 2: Predicting Fine-Scale Daily NO2 for 2005-2016 Incorporating OMI Satellite Data Across Switzerland

Next to aircraft noise, which is the main exposure considered in this thesis, other environmental exposures need to be accounted for, such as air pollution. Chapter 4 presents an approach to calculate daily retrospective values of NO_2 levels for Switzerland at 100 m resolution from 2005 to 2016 following a multistage modelling process. Input predictor data included daily monitored NO_2 data across Switzerland from the Immissionsdatenbank Luft (IDB) Swiss Federal Office for the Environment 2011, satellite-based data from the Ozone Monitoring Instrument (OMI) [OMINOA Team 2016], modelled tropospheric NO_2 data, and further spatial and temporal predictor data (i.e. landuse, road traffic, meteorology). Linear mixed-effect models were use to model nationwide NO_2 at 1 × 1 km resolution. Applying a random forest model based on local spatio-temporal variables to predict the residuals from the previous modelling stage finally allowed to model NO_2 at 100 × 100 m resolution. This study serves as a proof of concept for the applicability of a method originally developed to predict particulate matter to predict daily NO_2 at similar spatial resolution. In addition, this study provides historical NO_2 data easily extractable and applicable to any day and location in Switzerland, facilitating future epidemiological research.

2.2.4 Part III: Acute cardiovascular mortality

Objective 3: Does nighttime aircraft noise trigger mortality? A case-crossover study on 24'886 cardiovascular deaths

Using the aircraft noise exposure metrics especially calculated for the case-crossover study design for the SNC population located around Zurich described in Chapter 3, we investigated the role of the specific night-time exposure windows on acute cardiovascular mortality. We estimated the odds ratio of cause-specific cardiovascular mortality using conditional logistic regression and adjusted for NO_2, $PM_{2.5}$, temperature, precipitation, and holidays. Night-time aircraft noise was modelled using penalized splines in order to describe the shape of the association between aircraft noise and acute cardiovascular mortality. Separate models were created for each exposure metric and window of interest. Finally, we used categorical models to quantify the odds ratio associated with different aircraft noise exposure levels and calculated the population attributable fraction for night-time aircraft noise (2h-L_{Aeq}). Stratified analyses on individual characteristics such as gender, age groups, education, socio-economic position, and housing was conducted to identify possible effect modification of association between acute aircraft noise exposure and cardiovascular mortality.

Objective 4: Acute cardiovascular mortality with warm and cold temperatures in Switzerland: a case-crossover study

In Chapter 6, we estimated the risk of cause-specific cardiovascular death associated with heat and cold using distributed non-linear lag models. Taking advantage of the database created to address objective 3, daily temperature and precipitation data were available at 2 × 2 km, at 2 m above ground level from MeteoSwiss [MeteoSwiss 2017; MeteoSwiss 2016]. We modelled the relationship between daily average mean temperature and cause-specific cardiovascular mortality using a lag structure up to 7 and 14 days before death for warm and cold respectively. We estimated the odds ratio of mortality as the deviation from the empirically derived optimum temperature (20°C) to the 99^{th} percentile (34°C) of the annual mean temperature distribution for heat and from the optimum temperature to the 5^{th} percentile (-3°C) for cold. We conducted stratified analyses to investigate effect modification by individual characteristics (e.g. sex, age, socio-economic and marital status). Finally, we investigated the interaction between temperature and air pollution and aircraft noise on the association with all-cause car-

diovascular mortality by introducing interaction terms with NO_2, $PM_{2.5}$, and normalized aircraft noise, modelling 4-days average mean temperature as a second-degree polynomial. All models were fully adjusted for precipitation, NO_2, $PM_{2.5}$, aircraft noise, and holidays.

Objective 5: Mutual effects of particulate matter and nitrogen oxide on cause-specific acute cardiovascular mortality: a case-crossover study in Switzerland

As last investigated environmental exposure and based on the same study population and design than for objectives 3 and 4, we estimated the risk of cause-specific cardiovascular mortality associated with daily NO_2 and $PM_{2.5}$ exposure at home location. For this purpose, existing nationwide $PM_{2.5}$ at 100 $\times$ 100 m resolution were extended to the years 2014 and 2015 necessary to the present study. To investigate the delayed response of ambient air pollution on the risk of cardiovascular mortality, we used distributed lag models (DLNM) up to 7 days preceding death, adjusted for daily temperature, night-time aircraft noise, firework, and holidays and built separate models for NO_2 and $PM_{2.5}$ respectively. Mutual confounding between the two air pollutants and further confounding by short-term environmental exposures (i.e. night-time aircraft noise and mean temperature) was assessed by removing individual exposures from the overall distributed lag models. Finally, simplified models were created using average exposure from lags 0-4 for both NO_2 and $PM_{2.5}$ as identified from the DLNM to investigate individual and social susceptibilities introducing individual interaction terms for different subgroups of the population (e.g. age, sex, education, socio-economic status). This approach resulted in a single multiple-exposures model, capturing the individual contribution of different environmental exposures on cardiovascular mortality, based on exposure metrics and timings identified in the individual chapters.

2.3 Ethical statement

This research was funded by the Swiss National Fund (SNF), grand number 324730_173330. The use of the SNC data for this study was approved by the cantonal ethics boards of Bern (KEK No 205/06) and Zürich (KEK No 13/06).

Part II

Exposure assessment

Chapter 3

Individual Aircraft Noise Exposure Assessment for a Case-Crossover Study in Switzerland

Apolline Saucy[1,2], Beat Schäffer[3], Louise Tangermann[1,2], Danielle Vienneau[1,2], Jean-Marc Wunderli[3], Martin Röösli[1,2]

[1] Swiss Tropical and Public Health Institute (Swiss TPH), Basel, Switzerland

[2] University of Basel, Basel, Switzerland

[3] Swiss Federal Laboratories for Materials Science and Technology (Empa), Dübendorf, Switzerland

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Individual Aircraft Noise Exposure Assessment for a Case-Crossover Study in Switzerland †

Apolline Saucy [1,2], Beat Schäffer [3], Louise Tangermann [1,2], Danielle Vienneau [1,2], Jean-Marc Wunderli [3] and Martin Röösli [1,2,*]

1 Swiss Tropical and Public Health Institute (Swiss TPH), CH-4002 Basel, Switzerland; apolline.saucy@swisstph.ch (A.S.); louise.tangermann@swisstph.ch (L.T.); danielle.vienneau@swisstph.ch (D.V.)
2 Faculty of Science, University of Basel, CH-4003 Basel, Switzerland
3 Empa, Swiss Federal Laboratories for Materials Science and Technology, CH-8600 Dübendorf, Switzerland; beat.schaeffer@empa.ch (B.S.); jean-marc.wunderli@empa.ch (J.-M.W.)
* Correspondence: martin.roosli@swisstph.ch (M.R.)
† This paper is an extended version of our paper published in the proceedings of the Inter-Noise 2019 Conference on Noise Control for a Better Environment (INTERNOISE 2019, Madrid, Spain, 16–19 June 2019).

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Abstract: Accurate exposure assessment is essential in environmental epidemiological studies. This is especially true for aircraft noise, which is characterized by a high spatial and temporal variation. We propose a method to assess individual aircraft noise exposure for a case-crossover study investigating the acute effects of aircraft noise on cardiovascular deaths. We identified all cases of cardiovascular death (24,886) occurring near Zürich airport, Switzerland, over fifteen years from the Swiss National Cohort. Outdoor noise exposure at the home address was calculated for the night preceding death and control nights using flight operations information from Zürich airport and noise footprints calculated for major aircraft types and air routes. We estimated three different noise metrics: mean sound pressure level (L_{Aeq}), maximum sound pressure level (L_{Amax}), and number above threshold 55 dB (NAT_{55}) for different nighttime windows. Average nighttime aircraft noise levels were 45.2 dB, 64.6 dB, and 18.5 for L_{Aeq}, L_{Amax}, and NAT_{55} respectively. In this paper, we present a method to estimate individual aircraft noise exposure with high spatio-temporal resolution and a flexible choice of exposure events and metrics. This exposure assessment will be used in a case-crossover study investigating the acute effects of noise on health.

Keywords: exposure assessment; case-crossover; aircraft noise; cardiovascular diseases

1. Introduction

Noise from road, railway and air traffic is one of the most widespread sources of environmental stress and discomfort in everyday life [1,2]. The impact of aircraft noise on health has been increasingly recognized—especially in relation to long-term annoyance, sleep disturbance, and cardiovascular health outcomes. For instance, the Swiss Government recently established a national plan aiming to limit noise at source to promote population health, especially in the urban environment [3]. The Swiss Noise Abatement Ordinance of 1986 defines exposure limits for traffic noise and other technical noise sources. It limits permissible emissions at the source and contains building restrictions for areas exceeding the noise limits [4]. The World Health Organization (WHO) recently released new guidelines recommending that the average nighttime exposure to aircraft noise should stay below 40 dB [5]. A previous study conducted in the Swiss population reported an increased risk of death from myocardial infarction associated with long-term exposure to traffic noise. For an increase of 10 dB L_{den}

Abstract

Accurate exposure assessment is essential in environmental epidemiological studies. This is especially true for aircraft noise, which is characterized by a high spatial and temporal variation. We propose a method to assess individual aircraft noise exposure for a case-crossover study investigating the acute effects of aircraft noise on cardiovascular deaths. We identified all cases of cardiovascular death (24,886) occurring near Zürich airport, Switzerland, over fifteen years from the Swiss National Cohort. Outdoor noise exposure at the home address was calculated for the night preceding death and control nights using flight operations information from Zürich airport and noise footprints calculated for major aircraft types and air routes. We estimated three different noise metrics: mean sound pressure level (L_{Aeq}), maximum sound pressure level (L_{Amax}), and number above threshold 55 dB (NAT_{55}) for different nighttime windows. Average nighttime aircraft noise levels were 45.2 dB, 64.6 dB, and 18.5 for L_{Aeq}, L_{Amax}, and NAT_{55} respectively. In this paper, we present a method to estimate individual aircraft noise exposure with high spatio-temporal resolution and a flexible choice of exposure events and metrics. This exposure assessment will be used in a case-crossover study investigating the acute effects of noise on health.

Introduction

Noise from road, railway and air traffic is one of the most widespread sources of environmental stress and discomfort in everyday life [World Health Organization 2011; Münzel et al. 2020a]. The impact of aircraft noise on health has been increasingly recognized — especially in relation to long-term annoyance, sleep disturbance, and cardiovascular health outcomes. For instance, the Swiss Government recently established a national plan aiming to limit noise at source to promote population health, especially in the urban environment [Swiss Confederation 2017]. The Swiss Noise Abatement Ordinance of 1986 defines exposure limits for traffic noise and other technical noise sources. It limits permissible emissions at the source and contains building restrictions for areas exceeding the noise limits [Swiss Confederation 2019]. The World Health Organization (WHO) recently released new guidelines recommending that the average nighttime exposure to aircraft noise should stay below 40 dB [World Health Organization 2018b]. A previous study conducted in the Swiss population reported an increased risk of death from myocardial infarction associated with long-term exposure to traffic noise. For an

increase of 10 dB L_{den} (day-evening-night level, where evening levels get a 5 dB and night a 10 dB penalty), the hazard ratios were 1.04 (95% confidence interval: 1.02–1.06), 1.02 (1.01–1.03), and 1.03 (1.01–1.05) for road traffic, railway, and aircraft noise, respectively [Héritier et al. 2017]. Aircraft noise has also been shown to be associated with increased risk of hypertension, cardiovascular diseases and hospital admissions [Jarup et al. 2008; Correia et al. 2013; Hansell et al. 2013]. For ischemic heart disease, the recent WHO environmental noise guideline reports a risk ratio of 1.09 (1.04–1.15) per 10 dB L_{den} increase in aircraft noise [World Health Organization 2018b].

While experimental studies tend to increasingly draw attention to the short-term effects of noise — including aircraft noise — on sleep disturbance [Röösli et al. 2019; Griefahn, Marks, and Robens 2008], blood pressure [Schmidt et al. 2015; Huang et al. 2015], glucose and other metabolic perturbations [Münzel et al. 2020a; Eze et al. 2017], most of the existing epidemiological studies investigating the effects of noise on mortality focus on chronic noise exposure [World Health Organization 2011; Kempen et al. 2018; Héritier et al. 2017]; and thus less is known about the acute effects of transportation noise on cardiovascular mortality. It is particularly important to consider the timing of noise exposure when investigating the acute effects of transportation noise on health, including potential physiological differences in the different sleep phases during the night [Münzel et al. 2020a], as well as possible differences in the effects of transportation noise on sleep and mortality during various parts of the night [Griefahn, Marks, and Robens 2008; Héritier et al. 2018]. In this regard, the daily variations in flight schedules and routes present in many airports offer an appealing opportunity to conduct case-crossover studies to investigate the acute effects of aircraft noise on mortality.

In addition to the question of timing, particular attention should be paid to environmental noise characteristics and metrics. Noise exposure is complex, with high temporal and spatial variation, where a simple estimate of the daily mean might lead to a loss of important components of noise characteristics when investigating short term effects [Wunderli et al. 2016]. This potential source of error or misclassification can have consequences on the observed physiological response, which in turn will reduce explained variance. For instance, Héritier et al. showed that novel exposure metrics such as the intermittency ratio could account for temporal variations observed between different sources of traffic noise [Héritier et al. 2017]. Another recent study highlighted the importance of several noise metric combinations and the number of events to account for the observed annoyance associated with aircraft noise exposure [Haubrich et al. 2019].

In order to investigate the individual role of various nighttime exposure windows and metrics, a reliable and detailed noise exposure assessment is required.

The aim of this paper is to describe a methodology to calculate individual aircraft noise exposures for various time windows, required to conduct a case-crossover study investing effects of aircraft noise on myocardial infarction, stroke and other ischemic cardiovascular causes of mortality, in the framework of the TraNQuIL (Transportation Noise: Quantitative Methods for Investigating Acute and Long Term Health Effects) project. We propose a method to calculate several noise metrics that can be used individually and combined. This paper is an extended version of our conference proceedings published in [Saucy et al. 2019].

Materials and Methods

Case-Crossover Design

A case-crossover study is designed to investigate acute health effects from time-varying exposures such as air pollution, physical activity, emotional stress, or noise [Maclure and Mittleman 2000; Maclure 1991]. Analogous to a case-control study, the underlying question is how unusual the exposure situation is when an event occurs (case events) compared to the typical exposure when no event occurred (control events). Thus, exposure levels for case events are compared with exposure levels for control events as presented in Figure 3.1. It is a case-only study design with the advantage that it is not vulnerable to confounding from individual characteristics that are generally stable over a short period of time, such as age, gender or lifestyle factors [Maclure and Mittleman 2000]. Adjustment is typically required for a series of time-varying variables, such as air pollution or meteorological conditions. Since the first description of the case-crossover design by Maclure in 1991 [Maclure 1991], the framework has been commonly used to investigate the acute effects of various behavioral exposures, such as coffee intake or physical activity [Maclure and Mittleman 2000; Nawrot et al. 2011]. More recently, it has been increasingly applied to environmental exposures — mainly air pollution, but also wind turbine noise [Carracedo-Martínez et al. 2010; Poulsen et al. 2018]. The case-crossover design is very well suited to investigate environmental exposures, given sufficient temporal variation in exposure. Due to its extensive application in air pollution studies, potential bias and sampling strategies are well documented in this context [Janes, Sheppard, and Lumley 2005; Bateson and Schwartz 2001]. In brief,

the case-crossover framework is proposed as an alternative to time-series and data can be analyzed using conditional logistic regression. Since future environmental exposures are typically not influenced by the event status (for instance hospitalization or death), control events should be selected both before and after the event to reduce the risk of bias due to time trends in the exposure time-series [Lumley and Levy 2000; Mittleman, Maclure, and Robins 1995; Navidi 1998]. We propose to apply the same approach to investigate the acute effects of aircraft noise on mortality. At Zürich Airport (ZRH), meteorological conditions influence the daily flight schemes, offering day-to-day variability in individual noise exposure levels. As air operations may show weekly variation, we chose a time-stratified control sampling approach, where control events are matched on the day of the week within the same month, leading to 3–4 selected control events per case event, as described by Carracedo-Martínez et al. [Carracedo-Martínez et al. 2010].

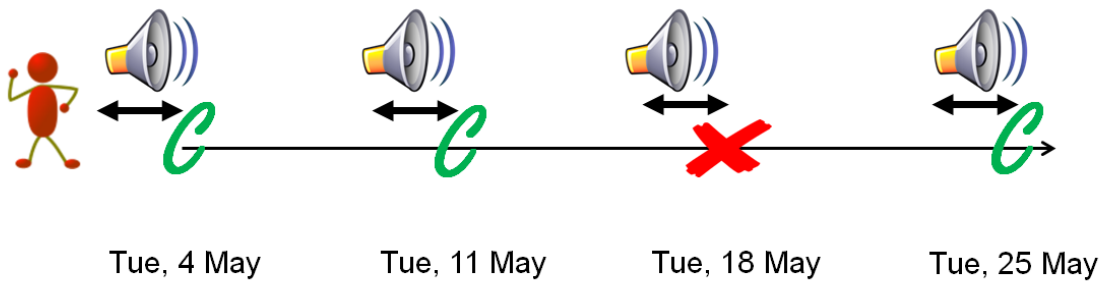

Figure 3.1: Example of case-crossover design, where exposure (noise level) is assessed in case (red) and control (green) event nights for an individual.

Zürich Airport

Zürich Airport (ZRH) is the largest airport in Switzerland in terms of air traffic. It is composed of a system of three runways, offering 12 major departure and four approach routes for commercial air traffic (see Figure 3.2). The assignment of air traffic to routes can change from day to day depending on different factors such as wind direction. Therefore, noise exposure at a given location is expected to vary between case and control days [Schäffer et al. 2011]. ZRH is subject to a flight ban, which limits the flight traffic to permitted exceptions such as emergency flights. The flight ban was set from 00:30 to 05:00 (approaches) and 06:00 (departures) in 2000 and extended to 23:30 to 06:00 in 2010 [Bissegger 2013].

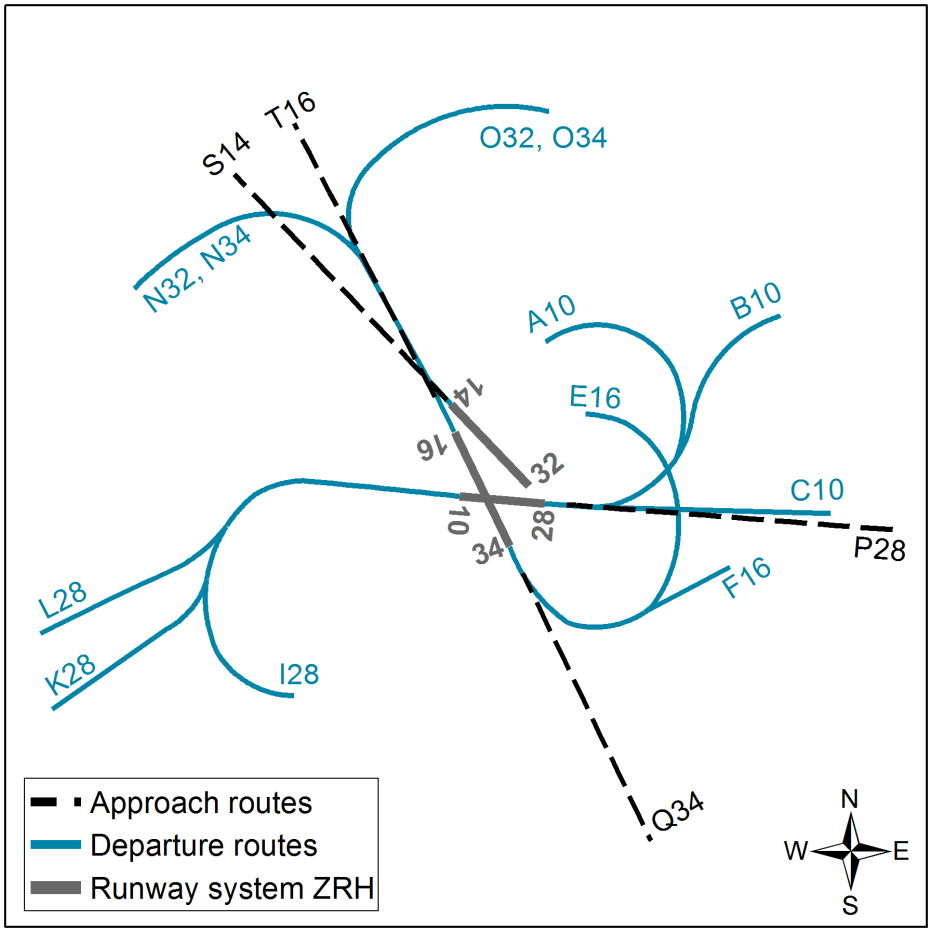

Figure 3.2: Overview of the runway system and air routes at Zürich Airport (ZRH).

Study Population

The study population was selected from the Swiss National Cohort (SNC) [Spoerri et al. 2010] in the vicinity of ZRH. It includes all individuals aged more than 30 years, dying from a cardiovascular cause (ICD10 classification I0 to I99) between 2000 and 2015. Only individuals potentially exposed to relevant aircraft noise exposure levels were selected. For this purpose, we used the envelope of the calculation perimeters for the Zürich Aircraft Noise Index (ZFI), which is a noise effect index for the number of highly annoyed and highly sleep disturbed persons (minimum L_{Aeq} of 47 dB during the day and/or 37 dB during the night) [Schäffer et al. 2012] (see Figure 3.3).

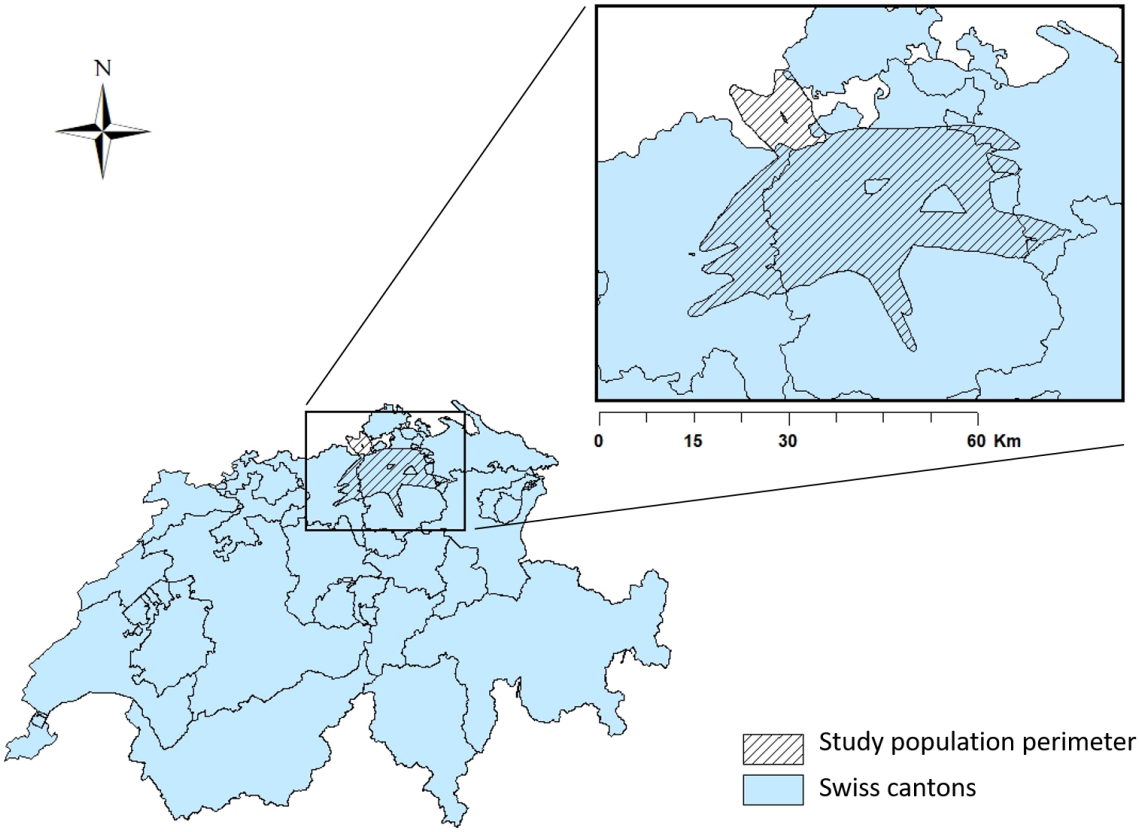

Figure 3.3: Overview of the study area used to select the study population around ZRH.

Geocoded residence at time of death were available from the SNC, together with other relevant personal information such as cause and time of death [Spoerri et al. 2010; Bopp et al. 2009].

The use of the SNC data for this study was approved by the cantonal ethics boards of Bern (KEK No 205/06) and Zürich (KEK No 13/06).

Noise Exposure Assessment

Individual exposure was determined at the home location for the night before death and for the control nights, within the same month. Only nighttime exposure to aircraft noise was assessed, focusing the investigation on the effects of noise on mortality during sleeping phases. In addition, home exposure is expected to represent the effective exposure more accurately during nighttime than daytime, as people are more likely to be at home. We calculated three different metrics for nighttime aircraft noise: (1) the

equivalent continuous sound pressure level (L_{Aeq}) (2) the mean A-weighted and slow-time-weighted maximal event level (L_{Amax}) and (3) the Number Above Threshold 55 dB (NAT_{55}). These three exposure metrics, used both individually and combined, were chosen to represent the energetic and intermittent characteristics of aircraft noise [Haubrich et al. 2019].

Two separate approaches were considered for death cases occurring during the night and cases occurring during the day. For individuals dying during the day (07:00–23:00), we considered different exposure windows in the night preceding death, which roughly represents sleeping behaviors at the population level — such as the hours when individuals typically fall asleep, are asleep (core night), and wake-up from sleep (early morning) — as used in previous studies investigating the chronic effects of noise on health [Héritier et al. 2018; Röösli et al. 2019]. In addition, the selected time windows are representative of the particular flight situation present at ZRH, such as the reduced air traffic period and the nighttime flight ban (see Table 3.1). For people dying during the night (23:00–07:00), noise exposure was calculated for the two hours preceding the death, in order to investigate potential triggering effects of noise within 2 h, as described for other exposures [Nawrot et al. 2011]. The different exposure windows for daytime and nighttime deaths are listed in Table 3.1. Case and control events were created for all selected case and control dates and their respective exposure windows, separately for daytime and nighttime deaths.

Table 3.1: List of the five different nighttime exposure windows considered for death case events occurring during the day and the night separately.

Exposure Time Window	**Description**	**Daytime Deaths 23:00 < 07:00**	**Nighttime Deaths 07:00 < 23:00**
19:00 < 23:00	Evening	X	
23:00 < 23:30	Early night (reduced air traffic) *	X	
23:30 < 06:00	Core night (flight ban)	X	
06:00 < 07:00	Early morning	X	
23:00 < 07:00	Overall night	X	
2 h	2 h preceding time of death		X

*Reserved for delayed flights

Lists of movements are available for 2000 to 2015 and include detailed information for all aircraft departures and arrivals at ZRH, such as aircraft type, air route, runway and time of departure or landing. The departure or landing time is defined as the moment of aircraft touch down or brake release. An additional 10 min buffer was added before

landing times and after departure times to account for the moment when the aircraft was perceived by the study population more distant from the airport. Some flights have missing information for the aircraft type and/or the air route. Using the tail number of the aircraft and the date of the event, missing aircraft types were retrieved. We selected only large aircraft types (>8618 Kg), as air traffic of small aircraft is negligible during the night.

As acoustic input, we used so-called footprints of aircraft noise events, previously calculated on a yearly basis at the authors' institution, Empa [Pietrzko et al. 2010]. A footprint corresponds to a 250 m receiver grid of mean noise exposure levels per aircraft type and air route. Each footprint is specific for a certain year, aircraft type (or group of aircraft types with similar flight performances), procedure (departure or arrival), air route, and possibly the time of day (e.g., day, night). Calculations were done with the aircraft noise calculation program FLULA2 [Pietrzko et al. 2010] using individual flight trajectories as obtained from large radar data sets [Schäffer et al. 2011]. FLULA2 considers sound source data (sound emission level and directivity patterns) of individual aircraft types, numbers, and distributions of movements, detailed flight geometries, and topography. FLULA2 calculations represent standard atmospheric conditions [Krebs et al. 2004]. From the level-time-histories LA(t) of the individual flights, the L_{Amax} and sound exposure level L_{AE} (resulting in the total energy of an event) are calculated, from which indicators such as the L_{Aeq} or the L_{den} could be derived. As a result of the calculations, the above-mentioned noise footprints (L_{AE} and L_{Amax}) were stored.

All flights occurring during the previously described time windows were selected and joined to their respective case and control events. Using information on year, time, aircraft type, air route, and procedure contained within the list of movements, the respective footprints were identified. Each of the identified footprints — a footprint represents the average noise exposure for a number of flights of a certain aircraft type (or aircraft group) on a specific air route — were individually imported to collect the noise metrics of interest. The process was repeated for each footprint, so that each identified flight was associated with eight noise exposure values (4 nearest L_{AE} and L_{Amax}). In a situation where no footprint was found, it was replaced by a similar footprint from a different time or year.

For each flight event, the average L_{AE} and L_{Amax} at the residential geocode was calculated from the four nearest noise receiver grid points using Inverse Distance Weighting

(3.1).

$$f(d) = \left\{ \begin{array}{c} d_i > 0, L = \frac{\sum_{i=1}^{4}\left(L_i * \frac{1}{d_i}\right)}{\sum_{i=1}^{4}\left(\frac{1}{d_i}\right)} \\ d_{i,min} = 0, L = L_i \end{array} \right\} \quad (3.1)$$

d_i = distance to neighbour i

L = Noise metric (L_{AE} or L_{Amax})

L_i = Noise level at residential geocode i

For L_{AE}, the averaged noise levels of all events were energetically summed for case and control events exposure time windows (3.2).

$$LAE_i = \sum_{i=1}^{n}(LAE_i) = 10 * \log \sum_{i=1}^{n}\left(10^{\frac{L_{AE_i}}{10}}\right) \quad (3.2)$$

i = flight event i

n= number of flight events for each case and control event and each time window

Finally, the L_{Aeq} were calculated for the different time windows (3.3). The case and control events for which no flight was found or the final L_{Aeq} values were negative were set to zero dB.

$$L_{Aeq} = L_{AE} - 10 * \log\left(\frac{T}{t_0}\right) \quad (3.3)$$

T = time within each exposure time-window [second]

$t_0 = 1$ s

For L_{Amax}, the highest level of L_{Amax} observed within each case and control event window was defined as the maximum noise level. Additionally, the number of flights with a L_{Amax} value larger than 55 dB was counted, giving the Number Above Threshold, NAT_{55}. The different steps of noise exposure assessment are illustrated in Figure 3.4.

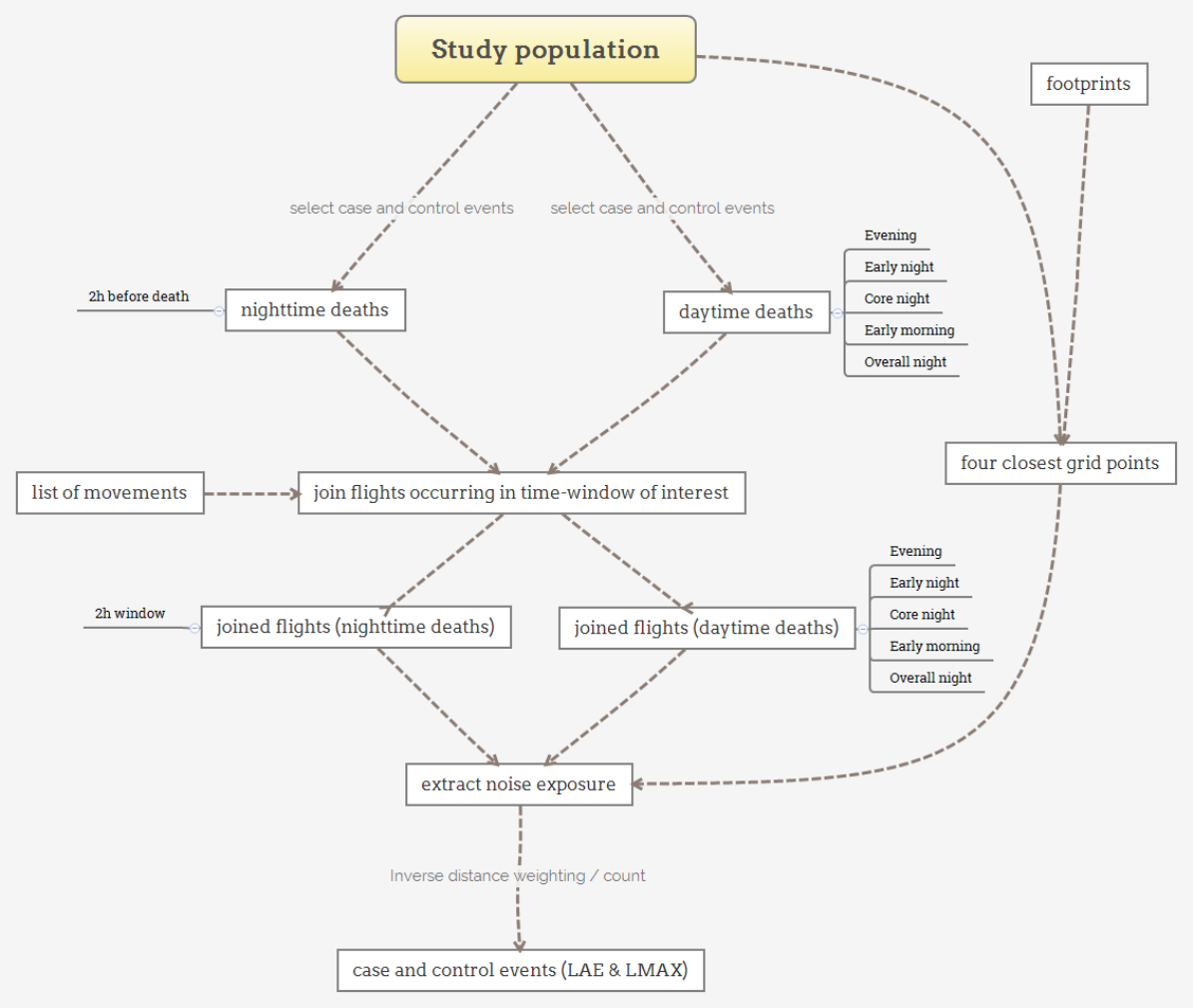

Figure 3.4: Graphical overview of the noise exposure assessment procedure.

Results

The above-described process resulted in the creation of a database listing individual aircraft noise exposure metrics (L_{Aeq}, L_{Amax}, and NAT_{55}) for each case and control event and time window of interest. Below, we give some exemplary results as calculated for our study population.

Overall, 4,664,132 flights started or landed at ZRH between 2000 and 2015. Only 216 flights were excluded because of missing air route information. Selecting only large aircraft starting or landing during the hours of interest (18:50–07:10) reduced the data to 1,124,748 flights.

Figure 3.5 shows the distribution of the L_{Aeq}, L_{Amax} and NAT_{55} exposure levels for 24,886 cases and 84,597 control events by time window, separately for day and night death events. For daytime deaths (Figure 3.5a), exposure was highest for the evening exposure window (19:00–23:00) and lowest during the core night (23:30–06:00) as expected for all three exposure metrics. Median L_{Aeq} of the different time windows ranged from 20 to 45 dB (max. 75 dB) and L_{Amax} median values from 40 to 60 dB (max. 100 dB). NAT_{55} ranged between 0 and 20 during the core night and between 0 and 160 for the evening exposure window. For the nighttime deaths (Figure 3.5b), median L_{Aeq}(2 h) was 36 dB with a maximum value about 65 dB and the average L_{Amax} was 57 dB with events up to 85 dB. The median NAT_{55} ranged between 0 and 75 flights for the 2 h exposure window preceding the time of case and control events.

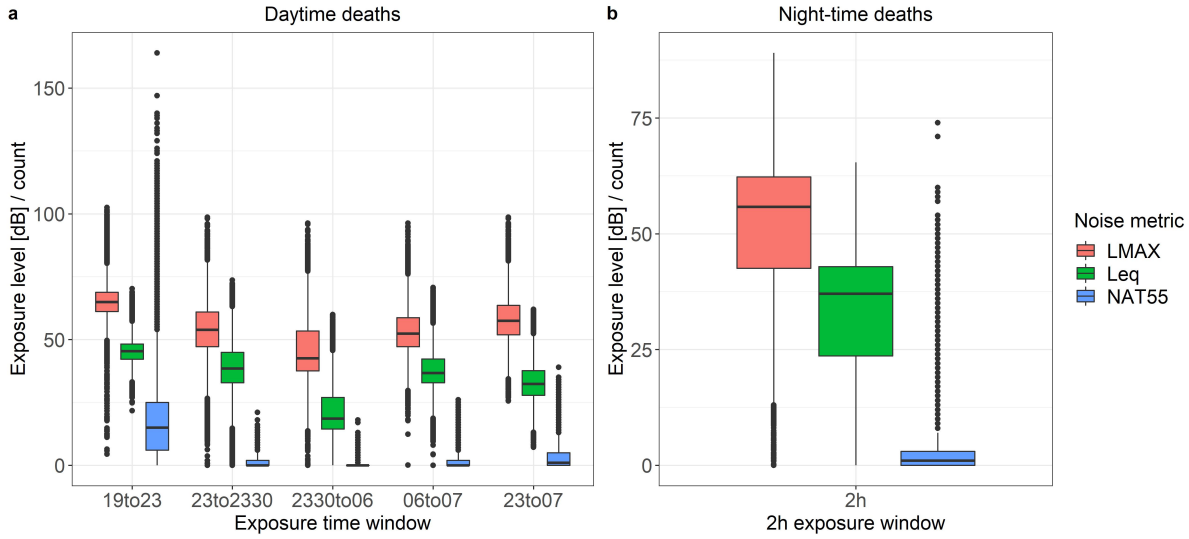

Figure 3.5: (**a**) Distribution of the noise exposure levels L_{Amax} and L_{Aeq} (in dB) as well as NAT_{55} (count) for the different time windows among all events (case and control) for daytime deaths, years 2000–2015. (**b**) Distribution of the noise exposure levels L_{Amax}, L_{Aeq} and NAT_{55} for the 2 h exposure window among the events (case and control) for nighttime deaths, years 2000–2015. The horizontal line of the box-plot represents the median value, the squares the interquartile range (IQR), and the whiskers the lower and upper limits (lower IQR value—1.5*IQR/upper IQR value + 1.5*IQR).

Discussion

Noise is a transient and quickly evolving exposure, which makes it different from other environmental exposures. Aircraft noise typically presents more variation over

time and according to WHO, the cardiovascular effects associated with aircraft noise exposure are also weaker than for road traffic noise [Kempen et al. 2018]. Therefore, it is particularly important to limit potential exposure misclassification. Accurate exposure assessment is needed to better understand the role of different noise characteristics and the timing of exposure on health outcomes.

In order to tackle these issues, we developed a method to assess individual aircraft noise exposures with a high temporal and spatial resolution to support a case-crossover epidemiological study design. We illustrate examples of exposure estimates for specific time windows within a selected population around ZRH having died from cardiovascular disease during 2000–2015, to be used in further epidemiological health studies. It uses a list of movements from ZRH and links them with previously calculated aircraft noise footprints for different aircraft types and air routes at various points in time. These calculations are based on validated simulations, using individual flight trajectories and radar data, and take into account the general topography. With this method, we could recreate individual aircraft noise exposure for a large population sample over a period of 2000 to 2015 and extract three different noise metrics to investigate and describe potential short-term health effects in further studies.

The novelty of the approach proposed here relies on the combination of using a case-crossover design to investigate the possible effects of aircraft noise on health and detailed aircraft noise calculation available for our study population. The case-crossover design is particularly well suited to investigate aircraft noise, as flight patterns around airports with a multi-directional runaway system vary from day to day, offering sufficient exposure variation. The choice of exposure events is very flexible and precise, which makes this an attractive approach for conducting case-crossover studies investigating short-term or transient effects of noise on health. This framework accounts for several potential individual confounders and reduces the risk of bias resulting from many individual characteristics. It is, however, more sensitive to time-varying exposures, such as air pollution and meteorological factors, which need to be adjusted for in further epidemiological studies. The case-crossover design can also be quite sensitive to the selection of control events and can potentially have an impact on temporal bias and overall power. When applied to environmental exposures, a bi-directional control sampling approach — like the time-stratified sampling scheme chosen in the present study — together with a choice of control referents matching the most important time-varying factors, enable to reduce temporal bias [Janes, Sheppard, and Lumley 2005].

the present paper, we propose a sampling scheme matched on the day of the week due to expected weekly variations in the flight schemes and health events. High data quality makes our exposure assessment precise, although some exposure misclassification may occur if people are not at home during the night. This would produce an underestimation of a true risk but not a false positive result if there were no association. Other individual varying factors, such as alcohol intake or physical exercise cannot always be taken into account in this retrospective cohort setting. Nevertheless, due to its differences towards other existing studies in the field — including in terms of strengths and limitations — this approach is likely to offer meaningful insights in our general understanding of the association between aircraft noise and mortality. It also offers the possibility to investigate several noise metrics and their possible combinations to improve our understanding of the relationship between aircraft noise and mortality. The aircraft noise footprints used in the present approach are specific for our study area. However, lists of movements should be easily available in other locations. The proposed method can be adapted and applied to many different settings and used as a precedent to assess individual aircraft noise exposure based on lists of airports' flight events.

Conclusions

We present a method to assess individual aircraft noise exposures with high temporal and spatial resolution. This method, especially designed to support a case-crossover study, represents a novel framework to investigate the short-term effects of aircraft noise on mortality. We propose to apply this approach to retrospective data and this paper may, therefore, serve as an exposure assessment method in large, long-term cohort settings. Due to its differences towards other study designs in terms of possible bias and confounding, this approach may complement previous research and bring meaningful insights in our general understanding of the acute physiological effects of noise.

Authors contributions: Conceptualization, A.S. and M.R.; methodology, A.S. and M.R.; A.S. and B.S. for individual aircraft noise exposure methodology.; formal analysis, A.S.; resources, M.R., J.-M.W. and B.S.; writing—original draft preparation, A.S.; writing—review and editing, M.R., D.V., B.S., J.-M.W., and L.T.; supervision, M.R.; funding acquisition, M.R. All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest: The authors declare no conflict of interest.

Chapter 4

Predicting Fine-Scale Daily NO_2 for 2005-2016 Incorporating OMI Satellite Data Across Switzerland

Kees de Hoogh[1,2], Apolline Saucy[1,2], Alexandra Shtein[3], Joel Schwartz[4], Erin A. West[5], Alexandra Strassmann[5], Milo Puhan[5], Martin Röösli[1,2], Massimo Stafoggia[6], and Itai Kloog[3]

[1] Swiss Tropical and Public Health Institute (Swiss TPH), Basel, Switzerland

[2] University of Basel, Basel, Switzerland

[3] Ben-Gurion University of the Negev, Beer Sheva, Israel

[4] Department of Environmental Health, Harvard T. H. Chan School of Public Health, Cambridge, United States

[5] Epidemiology, Biostatistics and Prevention Institute, University of Zurich, 8001 Zurich, Switzerland

[6] Department of Epidemiology, Lazio Regional Health Service,Rome, Italy

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Predicting Fine-Scale Daily NO_2 for 2005−2016 Incorporating OMI Satellite Data Across Switzerland

Kees de Hoogh,*[,†,‡] Apolline Saucy,[†,‡] Alexandra Shtein,[§] Joel Schwartz,[∥] Erin A. West,[⊥] Alexandra Strassmann,[⊥] Milo Puhan,[⊥] Martin Röösli,[†,‡] Massimo Stafoggia,[#] and Itai Kloog[§]

[†]Swiss Tropical and Public Health Institute, 4002 Basel, Switzerland

[‡]University of Basel, 4001 Basel, Switzerland

[§]Department of Geography and Environmental Development, Ben-Gurion University of the Negev, P.O. Box 653, Beer Sheva 8410501, Israel

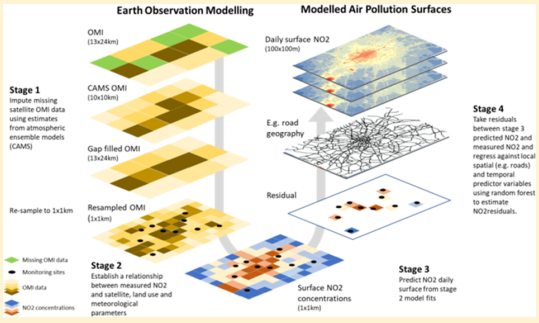
[∥]Department of Environmental Health, Harvard T. H. Chan School of Public Health, Cambridge, Massachusetts 02115, United States

[⊥]Epidemiology, Biostatistics and Prevention Institute, University of Zurich, 8001 Zurich, Switzerland

[#]Department of Epidemiology, Lazio Regional Health Service, 00147 Rome, Italy

Supporting Information

ABSTRACT: Nitrogen dioxide (NO_2) remains an important traffic-related pollutant associated with both short- and long-term health effects. We aim to model daily average NO_2 concentrations in Switzerland in a multistage framework with mixed-effect and random forest models to respectively downscale satellite measurements and incorporate local sources. Spatial and temporal predictor variables include data from the Ozone Monitoring Instrument, Copernicus Atmosphere Monitoring Service, land use, and meteorological variables. We derived robust models explaining ∼58% (R^2 range, 0.56−0.64) of the variation in measured NO_2 concentrations using mixed-effect models at a 1 × 1 km resolution. The random forest models explained ∼73% (R^2 range, 0.70−0.75) of the overall variation in the residuals at a 100 × 100 m resolution. This is one of the first studies showing the potential of using earth observation data to develop robust models with fine-scale spatial (100 × 100 m) and temporal (daily) variation of NO_2 across Switzerland from 2005 to 2016. The novelty of this study is in demonstrating that methods originally developed for particulate matter can also successfully be applied to NO_2. The predicted NO_2 concentrations will be made available to facilitate health research in Switzerland.



INTRODUCTION

Nitrogen dioxide (NO_2) remains an important traffic-related pollutant associated with both short- and long-term health effects. Faustini et al.[1] performed a systematic review and meta-analysis of studies (between 2003 and 2014) investigating the long-term effect of ambient NO_2 concentrations on mortality. They found evidence that the effect of NO_2 on mortality is as great as that of $PM_{2.5}$ with a 4% increase of mortality per 10 $\mu g/m^3$ NO_2 (compared to a 5% increase per 10 $\mu g/m^3$ $PM_{2.5}$). A systematic review of Mills et al.[2] found evidence of an association between mortality and hospital admissions and short-term exposure to NO_2. Most health studies investigating short-term health effects to NO_2, however, are generally restricted by using crude short-term exposure estimates. They mainly use data from a single or multiple monitoring stations for an area/city,[3−6] thereby not capturing the within area/city spatial variation of NO_2.

More granulated NO_2 data with respect to specific locations, specific days, day-to-day variability, and longer periods of time are needed to fully exploit the potential of some health studies. For example, the LuftiBus campaign of Zurich Lung Association, a not-for-profit organization promoting prevention and treatment of lung diseases, performed spirometry tests in the general population of Switzerland from 1993 to 2012. By linking these data to the Swiss National Cohort (SNC), the health data were geocoded to the place of residence of the LuftiBus participants. To investigate the effect of short-term air pollution exposures on lung function, there is a need for high spatiotemporal air pollution estimates across Switzerland. However, to date, no daily NO_2 surfaces exist for Switzerland with sufficient

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Abstract

Nitrogen dioxide (NO_2) remains an important traffic-related pollutant associated with both short- and long-term health effects. We aim to model daily average NO_2 concentrations in Switzerland in a multistage framework with mixed-effect and random forest models to respectively downscale satellite measurements and incorporate local sources. Spatial and temporal predictor variables include data from the Ozone Monitoring Instrument, Copernicus Atmosphere Monitoring Service, land use, and meteorological variables. We derived robust models explaining ∼58% (R^2 range, 0.56–0.64) of the variation in measured NO_2 concentrations using mixed-effect models at a 1 × 1 km resolution. The random forest models explained ∼73% (R^2 range, 0.70–0.75) of the overall variation in the residuals at a 100 × 100 m resolution. This is one of the first studies showing the potential of using earth observation data to develop robust models with fine-scale spatial (100 × 100 m) and temporal (daily) variation of NO_2 across Switzerland from 2005 to 2016. The novelty of this study is in demonstrating that methods originally developed for particulate matter can also successfully be applied to NO_2. The predicted NO_2 concentrations will be made available to facilitate health research in Switzerland.

Introduction

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More granulated NO_2 data with respect to specific locations, specific days, day-to-day variability, and longer periods of time are needed to fully exploit the potential of some health studies. For example, the LuftiBus campaign of Zurich Lung Association, a not-for-profit organization promoting prevention and treatment of lung diseases, performed spirometry tests in the general population of Switzerland from 1993 to 2012. By linking these data to the Swiss National Cohort (SNC), the health data were geocoded to the place of residence of the LuftiBus participants. To investigate the effect of short-term air pollution exposures on lung function, there is a need for high spatiotemporal air pollution estimates across Switzerland. However, to date, no daily NO_2 surfaces exist for Switzerland with sufficient spatiotemporal resolution. Previously, de Hoogh et al. [De Hoogh et al. 2018] developed geostatistical hybrid models for $PM_{2.5}$ taking advantage of the MAIAC aerosol optical depth (AOD) data combined with other spatiotemporal predictor variables to estimate daily ambient $PM_{2.5}$ concentration at a 100 $\times$ 100 m spatial resolution for 2003–2013. The equivalent of AOD data for enhancement of daily NO_2 modeling is the Ozone Monitoring Instrument (OMI) NO_2 data product. Despite the coarse spatial resolution of the OMI data, 13 $\times$ 24 km, these data could help explain part of the spatiotemporal variation observed in the daily NO_2 measurements. Compared to the number of studies integrating AOD data in geostatistical models to estimate PM concentrations, very few have done so for NO_2 using OMI data.

Lamsal et al. [Lamsal et al. 2008] described the potential of OMI-retrieved tropospheric NO_2 columns to infer ground-level NO_2 concentrations at different spatial and temporal scales over Northern America by applying scaling factors from GEOSChem. Since then, recent studies have shown that satellite NO_2 data improved annual and/or seasonal land use regression models at the regional [Yang et al. 2017], national [Young et al. 2016; Bechle, Millet, and Marshall 2015; Hoek et al. 2015; Knibbs et al. 2014; Novotny et al. 2011], continental [Vienneau et al. 2013; De Hoogh et al. 2016], and global [Larkin et al. 2017] scales. The few studies using satellite-derived data to develop daily NO_2 models thus far were carried out by Lee et al. [Lee and Koutrakis 2014] and Zhan et al [Zhan et al. 2018] who used OMI data to estimate daily NO_2 concentrations in New England, USA, for the years 2005–2010 and in China for 2013–2016, respectively.

A challenge of using satellite-derived data for modeling is missing data, mainly due to cloud cover. Recently, Stafoggia et al. [Stafoggia et al. 2019] have succeeded in pioneering a method to impute missing AOD using estimates from atmospheric ensemble

models. To our knowledge, this methodology has not yet been applied to impute missing OMI NO_2 and include this as a novel aspect of this article.

We describe the modeling of daily average NO_2 concentrations using spatial and temporal predictor variables through the following four-stage process: (1) imputation of missing OMI NO_2 concentrations (mainly due to cloud cover) using ensemble CAMS predicted total column nitrogen dioxide/nitrogen oxides modeled data within a mixed-effect model; (2) establishing a relationship between surface NO_2 measurements and OMI together with large-scale spatiotemporal predictors allowing prediction of spatially continuous NO_2 concentrations using a mixed-effect model; (3) predicting NO_2 concentrations at a global scale using the model fit of stage 2; and (4) explaining the spatial and temporal variation in the residuals between the global NO_2 estimates and the measured surface NO_2 concentrations using fine local predictor variables in a random forest (RF) framework. The final fine-scale daily NO_2 surfaces are a combination of the global-scale NO_2 predictions and the fine-scale explained residual predictions.

Materials and Methods

NO_2 Monitoring Data

Daily NO_2 monitoring data, measured using the chemiluminescent (majority of sites) and the differential optical absorption spectroscopy methods, from 2005 to 2016, were obtained from the Immisionsdatenbank Luft (IDB) (IDB Luft, Swiss Federal Office for the Environment 2011). Table S1 shows the number of NO_2 sites for each year, the number of daily observations, and a summary statistics of the NO_2 concentrations. We only selected sites with 30 daily measurements or more at a given site. The number of NO_2 monitoring sites increased from 67 (23,958 daily observations) in 2005 to 110 in 2016 (38,229 daily observations). Supplementary Figure S1 shows the spatial distribution of the monitoring sites in 2005 and 2016. The cities are well covered in both years with an increase in more rural sites seen in 2016. Measured NO_2 concentrations decreased slightly over the 12-year period with a mean NO_2 concentration of 27.6 $\mu g/m^3$ in 2005 to 23.2 $\mu g/m^3$ in 2016.

Satellite Data

The satellite-based NO_2 product is derived from the Ozone Monitoring Instrument (OMI) onboard the Aura satellite platform. The OMI onboard the NASA EOS-Aura satellite, which was launched in 2004, is a nadir-looking, push broom ultraviolet–visible (UV–vis) solar backscatter grating spectrometer that measures the Earth's radiance spectrum from 270 to 500 nm with a resolution of approximately 0.5 nm. The 114° viewing angle of the telescope translated to a 2600 km wide swath on the Earth's surface enables measurements with a daily global coverage. The instrument has proven to be very stable with minimal degradation over the past 14 years [Levelt et al. 2018]. The OMI NO_2 Data Product version 3.0 (OMI/Aura Nitrogen Dioxide (NO_2) Total and Tropospheric Column 1-orbit L2 Swath 13 × 24 km V003) was obtained from the Goddard Earth Sciences Data and Information Services Center (https://disc.gsfc.nasa.gov) for 2005 to 2016. The OMINO2 retrieval algorithm for this version (v003) was improved from the previous versions 1, 2.1, and 2.2 by the following: (1) an improved algorithm for retrieving slant column densities; (2) including information from current or previous month's solar irradiance measurements to calculate stable solar irradiances; and (3) improvements to the Global Modelling Initiative (GMI) chemical transport model by an increased spatial resolution, an updated emission inventory, updated meteorological fields, and updated chemical and photochemical reaction rates [OMINOA Team 2016]. For the purposes of this study, the variable "ColumnAmountNO2TropCloudScreened" from the level-3 gridded OMNO2d was extracted.

Modeled Tropospheric Column Amount NO_2

For 2005 to 2016, we obtained daily estimates of near-real-time analysis and forecasts of global atmospheric composition from Copernicus Atmosphere Monitoring Service (CAMS) Reanalysis. We downloaded daily total column nitrogen oxides (January 2005–September 2014) and total column nitrogen dioxides (September 2014–December 2016) at 0.125° × 0.125° resolution (around 10 × 10 km) from the European Centre for Medium-Range Weather Forecasts (ECMWF) representing 3 pm in the afternoon (time = 00:00:00, step = 15). The daily CAMS total column nitrogen dioxide estimates were linked to the coarser spatial resolution of OMI NO_2 product by aggregating it from its original resolution of 10 × 10 km to OMI's resolution of 13 × 25

km (using mean values).

Spatial Predictor Data

Predictor variables were extracted at three scales: (a) the OMI cell geography (ca. 13 × 24 km), (b) the intermediate scale (1 × 1 km), and (c) the local scale (100 × 100 m). We included predictor variables covering a range of potential emission sources. Road network and traffic intensity variables were included as a proxy for vehicle on-road emissions; land cover variables for non-road emission sources like industry and residential areas; and light at night as a proxy for human activity.

Detailed information can be found in the Supporting Information (Supplementary Table S2). In summary, for the OMI cell geography and the intermediate scale, the following predictor variables were extracted: length of major and all roads; percentage of total built-up area; and X and Y coordinates of the grid cell centroids. Additionally, for the 1 × 1 km grid cell for the intermediate scale, the mean altitude was extracted. At the local scale, the following spatial predictor variables were extracted within different buffers, including land use variables (percentage of residential, industrial, and commercial, total built-up, urban green, and natural area), altitude, traffic intensity, number of intersections, light at night, the normalized difference vegetation index (NDVI), and NOx emissions for the years 2005, 2010, and 2015, including agriculture, household, industry, traffic, and wood smoke emissions. Supplementary Table S2 additionally shows the buffer sizes, expected direction of effect, and for which scales each predictor variable was extracted. All of these variables have expected positive signs in the model development, except for land cover variables like urban green and natural land plus altitude and NDVI which we expect to have a negative sign.

Temporal Predictor Data

Daily meteorological parameters were obtained from the European Centre for Medium- Range Weather Forecasts (ECMWF). From the ERA-interim (global atmospheric reanalysis) data set at a 0.125° × 0.125° resolution, (10 × 10 km) daily boundary layer height (blh), 2 m temperature (t), 10 m U wind component, 10 m V wind component, total cloud cover, and total precipitation modeled for 3 pm in the afternoon (time

= 12:00:00, step = 3) were downloaded [Dee et al. 2011]. Wind direction (wd) and wind speed (ws) were, respectively, calculated from the U and V wind components as follows:

$$wd = \alpha \, tan\, 2\,(-u_{10},\ -v_{10})\,\frac{\pi}{180} \tag{4.1}$$

$$ws = \sqrt{{u_{10}}^2 + {v_{10}}^2} \tag{4.2}$$

For each of the three geographies (13 × 24 km, 1 × 1 km, and 100 × 100 m), meteorological parameters were extracted. For the OMI cell geography, mean boundary layer height and temperature were extracted by intersecting the ERA 10 × 10 km cells with the OMI 13 × 24 km cells and calculating the mean.

Spatiotemporal Statistical Four-Stage Modeling

The first stage is intended for imputing missing OMI data using the CAMS ensemble estimates and other spatial and temporal predictor variables. All variables were scaled before entering in the following linear mixed-effect model

$$\begin{aligned} OMI_{ij} = (\alpha + u_j) + (\beta_1 + v_j)\, CAMS_{ij} + \beta_2 Lon_i \\ +\beta_3 Lat_i + \beta_4 blh_{ij} + \beta_5 T_{ij} + \beta_6 Alt_i \\ +\beta_7 Tot\_bu_i + \beta_8 Maj\_rds_i \end{aligned} \tag{4.3}$$

- where OMI_{ij} denotes the amount of NO_2 in the tropospheric column measured by OMI onboard the Aura satellite (cloud screened) at cell i on day j;
- α is the fixed and u_j is the random daily intercept on day j;
- CAMS_{ij} is the mean of CAMS ColumnAmountNO2TropCloud- Screened in the grid cell i on day j. β_1 is the fixed slope, and v_j is the random slope on day j;
- Lon_i, Lat_i, blh_{ij}, T_{ij}, Alt_i, Tot_bu_i, and Maj_rds_i are the assigned values of, respectively, the longitude, latitude of the center of the OMI cell, the mean boundary layer height, mean temperature, altitude, the sum of length of major roads, and percentage of total built-up area within the OMI cell at grid cell i and day j, with corresponding fixed slopes β_2 to β_8.

Prior to converting OMI NO_2 product into ground-level NO_2 concentrations (stage 2), the enhanced OMI data were resampled from the initial 13 × 24 km OMI geography into a finer 1 × 1 km spatial resolution using bilinear interpolation (performed in R using raster package). Bilinear interpolation takes into account the centroid value from the four closest cells for calculating each new grid cell. This was done to create a regular grid (1 × 1 km). Doing so adds information from the wider environment and reduces or smoothes the coarse OMI pixels.

The second stage is to build a model turning OMI NO_2 product into ground-level NO_2. Again, a linear mixed-effect model was applied using the predictor variables calculated at the 1 × 1 km resolution

$$\begin{aligned} NO_{2,ij} = (\alpha + u_j) + (\beta_1 + uv_j)\, OMI_{ij} + \beta_2 OMI_{ij} + \beta_3 Lon_i \\ + \beta_4 Lat_i + \beta_5 blh_{ij} + \beta_6 T_{ij} + \beta_7 Wsp_{ij} + \beta_8 Prec_{ij} \\ + \beta_9 Totbu_i + \beta_{10} Majrds_i \end{aligned} \tag{4.4}$$

- where $NO_{2,ij}$ denotes the measured NO_2 concentration at site i on day j;
- α is the fixed and u_j is the random daily intercept on day j;
- OMI_{ij} denotes the amount of NO_2 in the tropospheric column measured by OMI onboard the Aura satellite (cloud screened) at site i on day j. β_1 is the fixed slope and v_j is the random slope on day j;
- OMI_{ij}, Lon_i, Lat_i, blh_{ij}, T_{ij}, Wsp_{ij}, $Prec_{ij}$, Tot_bu_i, and Maj_rds_i are the assigned values of, respectively, OMI NO_2, the longitude, latitude of the center of the 1 × 1 km grid cell, the boundary layer height, temperature, wind speed, precipitation, percentage of total built-up area, and the sum of length of major roads within the OMI cell at grid cell i and day j, with corresponding fixed slopes β_2 to β_{10}.

In the third stage, we use the model fits from stage 2 to predict NO_2 at the 1 × 1 km scale.

In the fourth stage, we model the local component at the 100 × 100 m scale by explaining the residual between the predicted NO_2 at stage 3 and measured NO_2 at the monitoring site. To accomplish this, we defined an RF model for each year where the

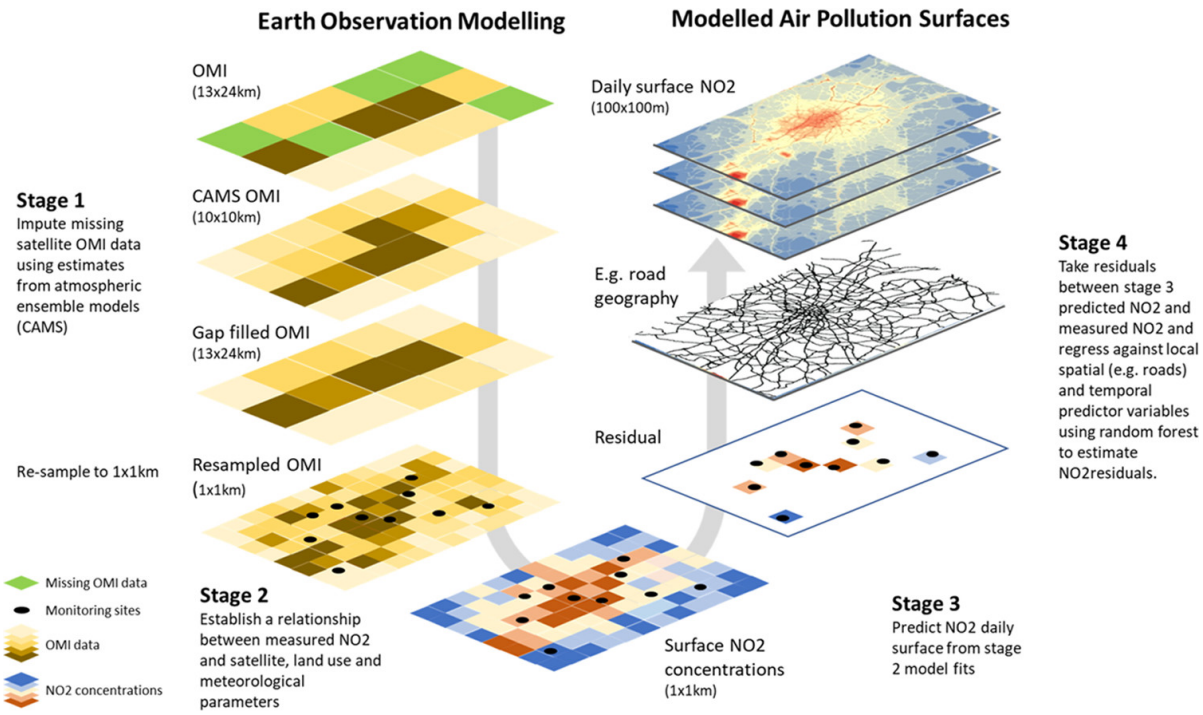

Figure 4.1: Stepwise modeling approach.

calculated daily NO_2 residuals are the target variables, and the predictor variables include the localscale (100 $\times$ 100 m) spatiotemporal variables, some of which have increasing buffer sizes. Figure 4.1 shows the flow diagram of the stepwise modeling approach.

Statistical Performance

The validation at every stage was performed using 10–fold cross-validation. The monitoring data were randomly divided into 90% training and 10% test data sets 10 times. Each time, we trained the model on 90% of the data and predicted NO_2 for the random 10% out-of-sample data. After completing this process and aggregating the 10 groups of the predictions that were made for the 10% out-of-sample data sets, this cross-validated prediction set was used for performance evaluation. To test the results for bias, we regressed the measured NO_2 values in each site and day against the corresponding cross-validated predictions. The following cross-validation statistics were calculated based on the crossvalidated predictions:

- Coefficient of determination (R^2) was used to evaluate the explained variance by the model. We computed three R^2 measures to evaluate the model's ability to

Table 4.1: Cross-Validated (CV) Performance Statistics Stage 1, 2, and 4 Modeling

		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Stage 1	R^2	0.714	0.699	0.653	0.673	0.667	0.716	0.703	0.678	0.679	0.623	0.712	0.678
	R^2 (cv)	0.688	0.675	0.634	0.661	0.644	0.701	0.692	0.657	0.655	0.612	0.696	0.662
	RMSE (cv)	0.557	0.570	0.600	0.575	0.592	0.538	0.564	0.596	0.583	0.625	0.555	0.590
	Intercept (cv)	-0.002	0.002	-0.003	0.003	0.000	-0.007	0.001	-0.004	-0.003	-0.003	0.001	-0.005
	Intercept standard error (cv)	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.004	0.003	0.003
	Slope (cv)	0.974	0.991	0.986	1.003	0.981	0.975	0.990	0.970	0.973	0.995	0.992	0.974
	Slope standard error (cv)	0.003	0.003	0.003	0.004	0.004	0.004	0.003	0.004	0.004	0.004	0.004	0.004
	R^2 space (cv)	0.921	0.910	0.900	0.891	0.896	0.907	0.913	0.902	0.888	0.882	0.912	0.877
	R^2 time (cv)	0.547	0.558	0.496	0.557	0.556	0.609	0.579	0.565	0.572	0.512	0.611	0.590
	RMSE space (cv)	0.155	0.158	0.165	0.166	0.150	0.145	0.159	0.153	0.150	0.169	0.150	0.161
	RMSE time (cv)	0.530	0.545	0.573	0.548	0.570	0.515	0.538	0.573	0.560	0.600	0.531	0.565
stage 2	R^2	0.595	0.635	0.575	0.595	0.577	0.597	0.563	0.565	0.583	0.559	0.573	0.562
	R^2 (cv)	0.580	0.621	0.555	0.583	0.561	0.587	0.551	0.548	0.561	0.546	0.560	0.548
	RMSE (cv)	10.748	10.994	11.077	10.697	11.113	10.855	11.273	11.063	11.169	10.228	10.948	10.113
	Intercept (cv)	-0.126	0.028	0.270	0.082	0.109	-0.169	-0.069	0.144	0.253	-0.073	-0.285	0.075
	Intercept standard error (cv)	0.168	0.141	0.141	0.127	0.130	0.126	0.134	0.128	0.128	0.124	0.130	0.119
	Slope (cv)	1.007	1.002	0.992	0.997	0.999	1.010	1.005	0.993	0.993	1.008	1.011	0.996
	Slope standard error (cv)	0.006	0.005	0.005	0.004	0.004	0.004	0.005	0.005	0.004	0.005	0.005	0.005
	R^2 space (cv)	0.525	0.603	0.508	0.514	0.471	0.521	0.471	0.461	0.476	0.511	0.482	0.468
	R^2 time (cv)	0.633	0.638	0.604	0.645	0.636	0.643	0.623	0.625	0.643	0.596	0.629	0.627
	RMSE space (cv)	7.910	7.386	8.165	7.780	8.057	7.602	8.333	8.143	8.080	7.707	8.159	7.587
	RMSE time (cv)	7.248	8.075	7.413	7.360	7.615	7.654	7.561	7.459	7.646	6.711	7.258	6.660
stage 4	R^2	0.743	0.726	0.752	0.724	0.728	0.699	0.751	0.731	0.728	0.740	0.743	0.753
	R^2 (cv)	0.748	0.727	0.752	0.725	0.727	0.693	0.756	0.728	0.729	0.738	0.749	0.752
	RMSE (cv)	5.308	5.548	5.407	5.542	5.690	5.844	5.504	5.709	5.717	5.132	5.421	5.011
	Intercept (cv)	-0.032	-0.054	-0.022	-0.008	-0.039	-0.076	-0.028	-0.043	-0.036	0.013	-0.018	-0.023
	Intercept standard error (cv)	0.034	0.032	0.030	0.029	0.029	0.030	0.028	0.029	0.029	0.026	0.029	0.026
	Slope (cv)	1.048	1.059	1.052	1.048	1.053	1.044	1.048	1.050	1.050	1.041	1.037	1.033
	Slope standard error (cv)	0.004	0.004	0.003	0.003	0.003	0.004	0.003	0.003	0.003	0.003	0.003	0.003
	R^2 space (cv)	0.999	0.997	0.998	0.998	0.998	0.997	0.999	0.998	0.998	0.998	0.998	0.998
	R^2 time (cv)	0.440	0.507	0.456	0.420	0.433	0.409	0.458	0.431	0.440	0.403	0.439	0.426
	RMSE space (cv)	5.245	5.473	5.329	5.470	5.612	5.761	5.434	5.619	5.640	5.072	5.361	4.962
	RMSE time (cv)	0.270	0.380	0.353	0.330	0.337	0.379	0.316	0.324	0.363	0.329	0.336	0.322

explain the variance for a different spatial and/or temporal level of the NO_2 data: (1) Total R^2 represents the explained variance of the daily NO_2 data by regressing the observed and predicted NO_2 values. (2) Spatial R^2 represents the contribution of the spatial variation to the total variance of the daily NO_2 model predictions over the whole study period. We averaged the daily observed and predicted NO_2 concentrations in each grid cell over the entire study period. R^2 was computed by regressing the study period average observed and predicted NO_2 values in each grid cell. (3) Temporal R^2 represents the contribution of the temporal variation to the total variance of the daily NO_2 model predictions across all monitoring stations and days. The whole study period predicted and observed averages were subtracted from the daily predicted and observed series of NO_2 concentrations. R^2 was then computed by regressing the daily observed and predicted NO_2 deviations (i.e., the residuals after subtraction of the mean).

- Root mean standard error (RMSE) — the square root of the mean quadratic differences between observed and predicted NO_2 values. It is a summary measure of

the prediction error, and it is on the same scale as the measured observation (NO_2, $\mu g/m^3$).

- Slope — the coefficient of the linear regression between observed NO_2 and predicted NO_2.
- All statistical analyses were performed in R Version 3.4.3. Extraction of GIS predictor variables was performed in ArcGIS 10.5 (ESRI).

Results and Discussion

Stage 1: Imputing Missing OMI Data Using CAMS Total Column Nitrogen Dioxide

Table 4.1 shows the performance of the stage 1 models. The models explained on average 68% (mean cross-validation $R^2 = 0.68$) of variability in the OMI data (R^2 range, 0.62–0.72); 90% of the variability was explained in the spatial term, whereas 56% was explained in the temporal term. The slope was close to 1 (mean slope = 0.984). The structure for models in all years is described in equation (4.3), except for the major roads variable, which was removed as it entered in each model with a negative sign. All of the other variables entered with the expected signs; total buildup area and longitude were positive, the other variables entered with a negative sign. A complete OMI database was built filling in the missing OMI data with the stage 1 models. Before stage 2, the OMI data were resampled to a 1 × 1 km raster using bilinear interpolation.

Second Stage: Building a Model Turning OMI into Ground-Level NO_2

In stage 2, the gap-filled resampled OMI data were linked to NO_2 monitoring sites and linear mixed-effect models were developed to predict NO_2 concentrations using the OMI data together with 1 × 1 km spatiotemporal predictor variables (see Table 4.1).

The linear effect models were able to explain on average 58% (R^2 range, 56–64%) of the variation in measured NO_2 concentrations (mean CV $R^2 = 0.57$). The spatial and temporal terms explained, respectively, 50 and 63% of the measured variance. Model structures differed slightly for the different years. The predictor variables sum major

roads, percentage total buildup, altitude, NDVI, wind speed, temperature, and precipitation entered all models. Boundary layer height entered all of the models except in the 2012 model; sum of all roads entered the 2006 and 2010–2016 models; percentage natural areas only entered 2006 and 2010.

Table 4.2: Relative Importance of Stage 4 Predictor Variables in Random Forest Models (10 Strongest Predictors Based on 12-Year Average)

Predictor variables	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	12 year average
Traffic intensity within 100m	13.30	8.37	10.96	13.76	11.62	10.66	11.02	12.18	13.89	12.83	13.70	14.66	12.25
Julian day	7.55	10.07	7.69	8.18	8.52	8.57	7.88	7.91	7.69	7.79	7.01	7.14	8.00
Boundary layer height	6.57	9.93	6.59	6.77	6.90	6.86	7.08	6.73	7.83	5.78	7.34	6.73	7.09
Wind direction	6.36	7.14	5.96	6.66	7.98	7.99	5.69	6.04	6.60	5.93	6.05	6.09	6.54
Temperature	6.22	7.41	6.27	6.03	6.83	6.79	6.25	6.14	6.17	5.61	5.71	5.53	6.25
Traffic intensity within 300m	7.58	5.14	10.26	5.75	4.20	4.37	4.37	4.30	4.55	6.17	6.66	6.60	5.83
Traffic emissions[a]	3.78	2.72	3.52	3.75	7.31	7.63	7.03	5.90	6.69	6.01	4.26	8.74	5.61
Wind speed	5.10	5.48	5.05	5.03	5.53	5.53	4.64	5.13	5.06	4.68	5.14	4.44	5.07
Traffic intensity within 500m	4.98	2.64	5.22	4.48	2.95	2.99	3.75	4.89	3.49	5.02	4.53	3.22	4.01
Precipitation	2.83	2.58	2.75	3.06	2.99	2.99	2.56	2.97	3.14	2.74	2.47	2.41	2.79

[a]2005 emissions used for 2005 –2007 models; 2010 emissions for 2008–2012; 2015 emissions for 2013–2016

Fourth Stage: Building Local Model on Residuals between Predicted NO_2 at Stage 2 and the Measured NO_2

We defined RF models for each year to explain the residuals between the modeled NO_2 at the 1×1 km scale and the monitoring site measurements with predictor variables extracted at the 100×100 m scale. The RF models explained on average 74% of variation in the residual NO_2 concentrations (spatial component $R^2 = 0.99$; temporal component $R^2 = 0.44$) using the parameters num.trees = 500 and mtry = 20 (R package Ranger). Table 4.2 shows the top 15 predictor variables in terms of average relative importance (%) over the 12 years. It shows dominance by traffic-related and meteorological variables. The main predictor variables at the local scale were traffic intensity within a 100×100 m buffer (12.25%), Julian day (8.0%), and boundary layer height (7.1%). Another three traffic indicators were included in the top 10: traffic intensity within 300 (5.83%) and 500 (4.01%) meters and traffic emissions (5.61%). The other variables in the top 10 were the meteorological parameters.

Figure 4.2 shows a series of maps depicting the variation in daily NO_2 concentrations at the 100×100 m resolution for 7 consecutive days in 2005 (Tuesday 8–Monday 14 February) across Switzerland. The same figure includes boxplots of measured daily NO_2

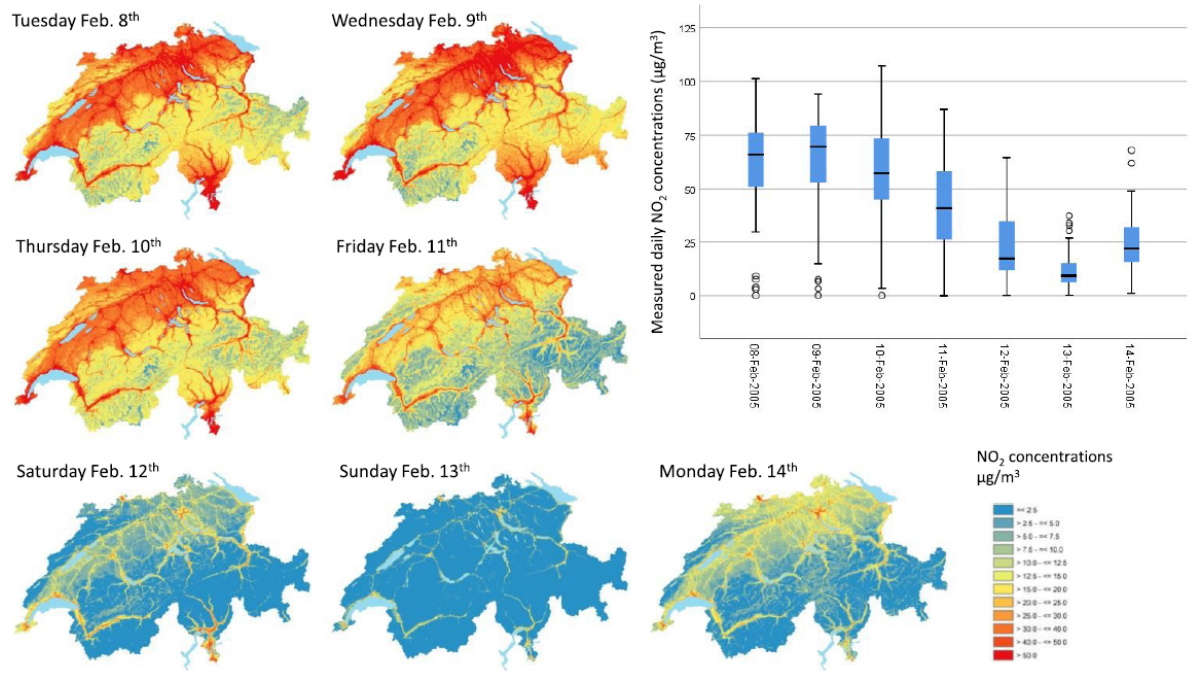

Figure 4.2: Estimated daily NO_2 concentrations at 100 × 100 m resolution for February 8–14, 2005 (maps) and boxplots of measured daily NO_2 at 65[a] operating monitoring stations for the same time period (graph). [a]64 stations for February 10 and 13.

concentrations during the same days in February 2005 using measurement data from approximately 65 monitoring stations. During this period, the mean measured NO_2 across the monitoring stations fluctuated from around 60 µg/m^3 during February 8 and 9 to 11 µg/m^3 on February 13, after which it increased again to 24 µg/m^3 on February 14. This trend is clearly replicated in the daily NO_2 maps. The data not only show the weekly cycle of pollution levels with higher levels measured and modeled during working days compared to the weekend but also the differences between days, mainly due to meteorological factors. A further check was carried out to determine whether a similar working day versus weekend difference was observed in the full measured NO_2 concentrations data set (2005–2016). As shown in Supplementary Table S3, we calculated the mean NO_2 concentrations for each day of the week and found a similar pattern, with lower measured NO_2 concentrations on Saturdays and Sundays (mean NO_2 = 23.07 and 18.77 µg/m^3, respectively) compared to working days (mean NO_2 concentrations ranging from 26.06 to 28.47 µg/m^3).

Discussion

This is the first study to apply the spatiotemporal modeling framework developed for $PM_{2.5}$ and AOD data (Figure 4.1) for NO_2. Specifically, we developed models to estimate daily NO_2 concentrations at a fine spatial scale of 100 × 100 m for 12 years from 2005 to 2016 across Switzerland. During the four-stage process, we applied a mixed-effect model to impute missing OMI using Total Column Nitrogen Dioxide retrieved from CAMS (1), established a relationship using a mixed-effect model between measured NO_2 and OMI plus spatiotemporal predictors at a 1 × 1 km scale (2), applied this model to estimate daily NO_2 across the full domain (3), and finally estimated local NO_2 concentrations at 100 × 100 m using RF explaining the residuals of the NO_2 measurements and the 1 × 1 km NO_2 estimates from stage 2 using local spatiotemporal predictor variables (4).

The stage 1 models explained on average 68% of variability in the OMI data (R^2 range, 0.62–0.72) for the years 2005–2016. The stage 2 linear mixed-effect models were able to explain on average 58% (range, 56–64%) of the variation in measured NO_2 concentrations. The RF models in stage 4 explained on average 74% (R^2 range, 0.70–0.75) of the overall variation in the residuals.

Spatial Variation in NO_2

The spatial pattern of estimated annual mean NO_2 concentrations is shown in Figure 4.3 for 2005 and 2016. High levels (>25 $\mu g/m^3$) are concentrated in urban centers including Zurich, Basel, Bern, Geneva, and Lugano, and along heavy traffic corridors, between the main cities and along the valleys in the mountainous areas. Low levels are observed in the rural areas with levels dropping to almost zero in the highaltitude areas of the Alps and the Jura. These spatial patterns remain similar between 2005 and 2016 with levels slightly lower in 2016.

Temporal Variation in NO_2

Figure 4.2 shows that the temporal variation in daily NO_2 concentrations can be large within 7 days (February 8–14, 2005). The boxplots in Figure 4.2 show the daily measured NO_2 from operating monitoring stations. The measured daily NO_2 concentration varies from approximately 70 $\mu g/m^3$ on February 8 and 9 (median NO_2 concentration of approximately 65 monitoring sites) to around 10 $\mu g/m^3$ on the 13^{th} and rising again

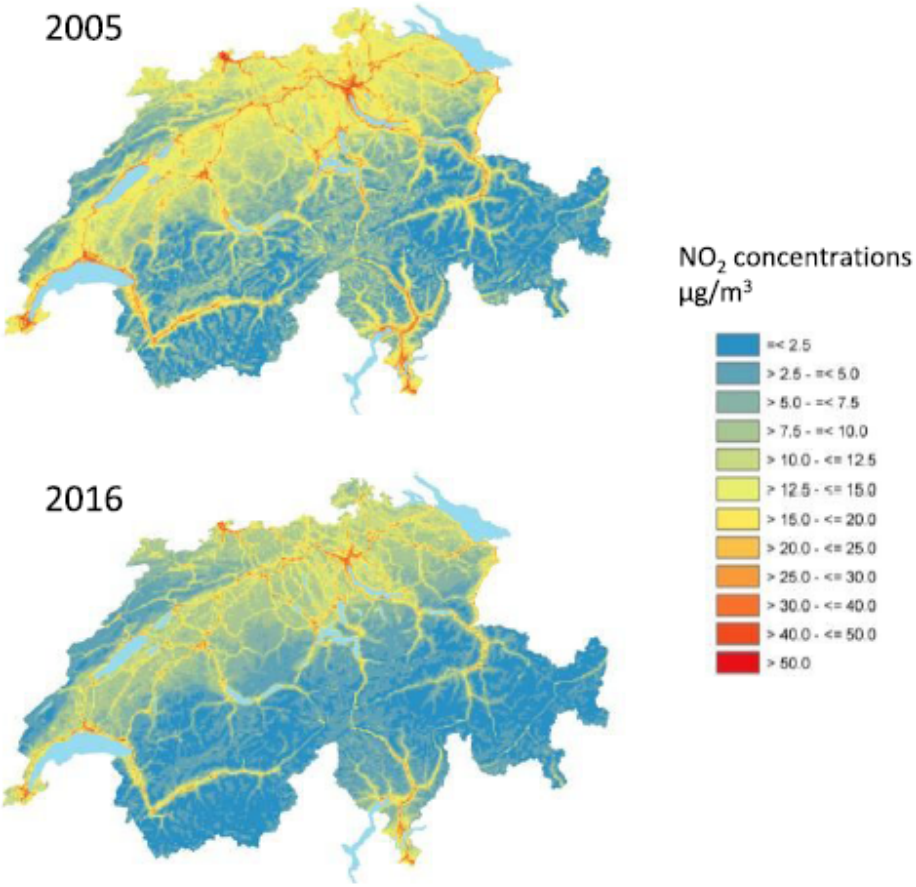

Figure 4.3: Estimated annual mean NO_2 concentrations ($\mu g/m^3$) for 2005 and 2016 at 100 $\times$ 100 m resolution.

to 24 $\mu g/m^3$ on the 14^{th} of February. The maps in Figure 4.2 replicate this trend with deep red colors on February 8 and 9 in the main cities, the Mittelland, and the valleys. Toward February 13, pollution levels decrease to an almost blue map. Even the small IQR in the boxplot for February 13 is matched by the map on the same day showing little spatial variation. This only illustrates 7 days of the 4017 days we modeled, but it shows the importance for health studies investigating short-term effects on, for instance, lung function or birth weight. The modeled daily NO_2 surfaces will allow these studies to calculate time-dependent exposure windows and thus better capture the day-to-day variation in their exposure estimation.

The annual NO_2 prediction maps for 2005 and 2016 (Figure 4.3) show that levels of NO_2 concentrations in Switzerland have only reduced slightly during the 11 years covered. The same trend is observed in measured mean NO_2 concentration data (Supplementary Table S1) showing a slight reduction from 27.6 µg/m3 in 2005 to 23.2 $\mu g/m^3$ in 2016.

Comparison with Other NO_2 Maps in Switzerland

No other daily maps for NO_2 are available for Switzerland. However, maps of annual mean NO_2 concentrations using dispersion modeling for 2005, 2010, and 2015 were previously published by the Federal Office for the Environment (FOEN) [Swiss Federal Office for the Environment 2011]. We calculated population-weighted NO_2 concentrations at the national scale and compared those to the reported population-weighted exposures for 2005, 2010, and 2015 in the FOEN report. Population-weighted NO_2 concentrations based on our annual NO_2 maps were 22.1, 21.4, and 19.1 $\mu g/m^3$ for 2005, 2010, and 2015, respectively, compared to 23.2, 20.8, and 18.9 $\mu g/m^3$ based on the FOEN maps. The remarkable match between both sets of population-weighted exposures shows how well the annual average NO_2 maps compare, using two very different methods (statistical versus dispersion model approach). This also gives us confidence about the validity of the daily NO_2 estimates, given that our annual average maps were calculated as the average of daily average NO_2 maps for each year.

Comparison with Other Studies

There are only a few studies modeling daily NO_2 concentrations over a large spatial domain using the OMI NO_2 product. Lee and colleagues integrated OMI NO_2 data in their land use regression models to estimate daily NO_2 concentrations [Lee and Koutrakis 2014]. They estimated daily NO_2 concentrations for the period 2005–2010 in the New England region, USA. Their mixed-effects model was able to explain 79% (cross-validated) of the variation in daily NO_2 concentrations measured at 22 monitoring sites. Apart from OMI NO_2, the model consisted of fine-scale land use variables and meteorological parameters. They concluded that the satellite remote sensing data helped to enhance the mixed-effects model. Since the Lee study, the OMI product has been improved to the OMI NO_2 Data Product version 3.0, which was used in the NO_2 modeling presented here. Zhan and colleagues also showed the potential of using the OMI NO_2 product as an input to a random forest spatiotemporal kriging model to estimate daily NO_2 concentrations across China at a $0.1^\circ \times 0.1^\circ$ grid (approximately 10

× 10 km) for 2013–2016 [Zhan et al. 2018]. Over the 4-year period, they were able to explain 62% of the daily variation and 73% of the spatial variation. In addition to NO_2 OMI, meteorological variables, day of the year, population density, and emissions were important variables. They used a two-stage model approach: (1) a random forest model to explain the NO_2 concentrations at the measurement sites using the aforementioned predictor variables and (2) kriging on the residuals of the measured NO_2 and predicted NO_2 from step 1.

Other studies modeling daily NO_2 concentrations without satellite NO_2 used a land use regression (LUR) approach supplemented with meteorological variables. Liu and colleagues explained, respectively, 51% and 43% of the spatial and temporal variability in NO_2 concentrations across the Changsha urban area in China for 2010 [Liu et al. 2015]. Johnson and colleagues estimated daily exposures to NO_2 by combining seasonal LUR models with daily routine monitoring data [Johnson et al. 2013]. This approach added 40% (summer) and 10% (winter) to the spatial variance compared to just using the monitoring data.

Limitations

Days with cloud cover is the reason for missing OMI NO_2 data. This is compounded by the coarse resolution of the OMI NO_2 data (13 × 24 km), classifying a grid cell as having missing data even if areas are cloud-free within the cell. We applied a novel imputation method using CAMS estimates of daily total column nitrogen oxides, available for all days, to fill in the OMI NO_2 gaps. This imputation method was successfully pioneered in an Italian study where it was used to impute missing data in MAIAC AOD data, using similar CAMS data. Here, we were also successful in filling in the gaps on OMI NO_2, the linear mixed-effects models explaining on average 68% of variability in the OMI data (R^2 range, 0.62–0.72), thus providing a robust base for imputation.

This study shows the potential for using earth observation data to develop robust models explaining fine-scale spatial (100 × 100 m) temporal (daily) variation of NO_2 across Switzerland from 2005 to 2016. The predicted NO_2 concentrations will be made available to facilitate health research in Switzerland. Further research is needed to investigate how well the methods work in larger countries and/or regions with potentially fewer ground monitoring sites.

On October 13, 2017, Copernicus Sentinel-5P was launched with the Tropospheric Monitoring Instrument (TROPOMI) onboard, the replacement of OMI. Operational data have been available since July 2018, with an improved resolution (3.5 $\times$ 7 km) compared to OMI (13 $\times$ 24 km). The TROPOMI product will allow continuation and enhancement of the spatiotemporal NO_2 modeling presented here, in Switzerland and beyond.

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Associated Content

The Supporting Information is available free of charge on the ACS Publications website. Statistics of daily NO_2 measurements, list of predictor variables, weekly cycle of measured NO_2 concentrations for 2005–2016, map of NO_2 monitoring sites (PDF).

Author Information:
Corresponding author:
E-mail: c.dehoogh@swisstph.ch. Tel: +41 (0)61 284 8749.
ORCID: Kees de Hoogh: 0000-0001-5974-2007
Notes: The authors declare no competing financial interest.

Part III

Acute cardiovascular mortality

Chapter 5

Does nighttime aircraft noise trigger mortality? A case-crossover study on 24,886 cardiovascular deaths

Apolline Saucy[1,2], Beat Schäffer[3], Louise Tangermann[1,2], Danielle Vienneau[1,2], Jean-Marc Wunderli[3], Martin Röösli[1,2]

[1] Swiss Tropical and Public Health Institute (Swiss TPH), Basel, Switzerland

[2] University of Basel, Basel, Switzerland

[3] Swiss Federal Laboratories for Materials Science and Technology (Empa), Dübendorf, Switzerland

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CLINICAL RESEARCH
Epidemiology and Prevention

Does night-time aircraft noise trigger mortality? A case-crossover study on 24 886 cardiovascular deaths

Apolline Saucy [1,2], Beat Schäffer [3], Louise Tangermann [1,2], Danielle Vienneau [1,2], Jean-Marc Wunderli [3], and Martin Röösli [1,2]*

[1]Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Socinstrasse 57, Basel 4002, Switzerland; [2]Faculty of Science, University of Basel, Petersplatz 1, Basel 4003, Switzerland; and [3]Empa, Swiss Federal Laboratories for Materials Science and Technology, Überlandstrasse 129, Dübendorf 8600, Switzerland

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Aims It is unclear whether night-time noise events, including from aeroplanes, could trigger a cardiovascular death. In this study, we investigate the potential acute effects of aircraft noise on mortality and the specific role of different night-time exposure windows by means of a case-crossover study design.

Methods and results We selected 24 886 cases of death from cardiovascular disease (CVD) from the Swiss National Cohort around Zürich Airport between 2000 and 2015. For night-time deaths, exposure levels 2 h preceding death were significantly associated with mortality for all causes of CVD [OR = 1.44 (1.03–2.04) for the highest exposure group (L_{Aeq} > 50 dB vs. <20 dB)]. Most consistent associations were observed for ischaemic heart diseases, myocardial infarction, heart failure, and arrhythmia. Association were more pronounced for females ($P = 0.02$) and for people living in areas with low road and railway background noise ($P = 0.01$) and in buildings constructed before 1970 ($P = 0.36$). We calculated a population attributable fraction of 3% in our study population.

Conclusion Our findings suggest that night-time aircraft noise can trigger acute cardiovascular mortality. The association was similar to that previously observed for long-term aircraft noise exposure.

* Corresponding author. Tel: +41 61 284 8383, Fax: +41 61 284 8501, Email: martin.roosli@swisstph.ch

Abstract

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Conclusion: Our findings suggest that nighttime aircraft noise can trigger acute cardiovascular mortality. The association was similar to that previously observed for long-term aircraft noise exposure.

Introduction

It is estimated that environmental noise exposure contributes to 48,000 new cases of ischaemic heart diseases (IHD) or 156,000 DALYs in Europe each year [European Environment Agency 2020; Kempen et al. 2018]. A meta-analysis performed for the new WHO noise guidelines considered all studies published until 2015 and reported that the risk for IHD increases by 8% per 10 dB increase in long-term road traffic noise [Van Kempen et al. 2018]. However, evidence for an association between aircraft noise and incidence of IHD and hypertension were rated of very low and low quality, respectively, due to the lack of longitudinal studies [Kempen et al. 2018; Van Kempen et al. 2018]. Since then several studies — including longitudinal — and meta-analyses investigated the cardiovascular health effects of aircraft noise [Vienneau et al. 2019; Weihofen et al. 2019], providing the evidence of associations with IHD [Pyko et al. 2019], including the incidence of hypertension (OR = 2.26 per 10 dB increase in L_{night} aircraft noise) [Dimakopoulou et al. 2017], myocardial infarction [Héritier et al. 2019; Seidler et al. 2016],

heart failure [Seidler et al. 2016], (ischaemic) stroke [Weihofen et al. 2019; Pyko et al. 2019; Héritier et al. 2019], and arrhythmias [Dimakopoulou et al. 2017]. It has also been suggested that night-time noise exposure is particularly relevant for cardiovascular health, through sleep disruption and initiation of physiological stress reaction [Münzel et al. 2020a; Héritier et al. 2018; Jarup et al. 2008].

While most epidemiological studies addressed cardiovascular effects of long-term exposure to transportation noise, there is a need to better understand whether noise exposure also acts as a trigger for cardiovascular events and how the timing of noise exposure modulates this response [European Environment Agency 2020; Vienneau et al. 2015]. Experimental studies have shown acute responses to environmental noise on different physiological responses, such as endothelial dysfunction [Schmidt et al. 2013], hypertension [Haralabidis et al. 2008; Münzel et al. 2014], and sleep quality [Röösli et al. 2019; Basner et al. 2008]. In the present study, we aim to investigate if and how night-time aircraft noise can trigger mortality for cardiovascular diseases (CVDs). We used mortality data from the Swiss National Cohort (SNC) over 15 years using a case-crossover design. We conducted separate analysis for night-time and daytime deaths and also tested three different noise exposure metrics to capture the characteristics and evolution of noise over time for various exposure windows.

Methods

Study design

We used a time-stratified case-crossover study design, in which each case of death was matched with up to four control days, chosen within the same month and same day of the week [Janes, Sheppard, and Lumley 2005]. The case-crossover design adjusts for any individual confounders that do not vary over a short period of time, such as age, smoking, or socio-economic status. This approach is particularly well suited to investigate acute risk effects with minimal bias [Maclure and Mittleman 2000] and has been largely applied to air pollution studies over the past two decades [Carracedo-Martínez et al. 2010].

With a focus on night-time noise exposure, we separately considered deaths occurring during the day (07:00–23:00), and deaths occurring during the night (23:00–07:00). For the night-time deaths, we considered a 2 h exposure window preceding death, as described for other triggers of acute cardiovascular mortality, such as air pollution and

coffee intake [Nawrot et al. 2011]. For daytime deaths, we investigated the effect of five different exposure windows defined a priori within the night preceding the day of event: overall night preceding the day of death (23:00–07:00); late evening (19:00–23:00); reduced air traffic reserved for delayed flights (23:00– 23:30); core night (23:30–06:00); and early morning (06:00–07:00).

Study population

The SNC is a long-term cohort based on the linkage of national census and mortality records for the whole Swiss population [Spoerri et al. 2010]. It contains personal information as well as household, building, and mortality data, including hour and cause of death [Panczak et al. 2012]. Based on a power analysis, we included mortality data from 4 December 2000 to 31 December 2015. We restricted the study population to adults over 30-year old with cardiovascular primary cause of death living near Zurich Airport (ZRH), using the envelope of the Zurich Aircraft Noise Index (ZFI) calculation perimeters from 2000 to 2016 for highly annoyed and highly sleep disturbed persons (Supplementary materials, Figures S1 and S2) [Schäffer et al. 2012]. We considered the following primary causes of death (International Classification of Diseases ICD-10): all CVD (ICD-10: I00–I99), IHD (ICD- 10: I20–I25), myocardial infarction (ICD-10: I21–I22), stroke (ICD-10: I60–I64), haemorrhagic stroke (ICD-10: I60–I62), ischaemic stroke (ICD- 10: I63), heart failure (ICD-10: I50), blood pressure related death (ICD-10: I10–I15), and arrhythmias (ICD-10: I44–I49).

Aircraft noise exposure

Individual exposure to aircraft noise was estimated at home locations for the relevant time windows on the selected case and control nights and exposure time windows as previously described elsewhere [Saucy et al. 2020b]. In short, we used a list of all aircraft movements at ZRH between 2000 and 2015 and linked them with pre-existing outdoor aircraft noise exposure calculations at 250 $\times$ 250 m resolution, specific for aircraft type, air route, time, and year [Pietrzko et al. 2010]. From these data, we calculated three noise exposure metrics: (i) average A-weighted equivalent continuous sound pressure level (L_{Aeq}), (ii) maximum sound pressure level (L_{Amax}), and (iii) number of events above threshold 55 dB (NAT_{55}) for the pre-defined time windows defined above. In addition, we extracted long-term night-time exposure to railway and road traffic noise (L_{night}) at

Table 5.1: Study population characteristics

Population characteristics	**Females (N=13,269)**	**Males (N=11,617)**
Time of death: N (%)		
Daytime	9,108 (70)	8,137 (70)
Nighttime 4,161 (30)	3,480	(30)
Age: mean (SD)	84 (9) 78	(12)
Education level: N (%)		
Compulsory or less	6,660 (50)	2,170 (18)
Upper secondary	5,756 (43)	6,597 (57)
Tertiary	521 (4)	2,629 (23)
Civil status: N (%)		
Single	1,154	(9) 923 (8)
Married	2,421	(18) 6,865 (59)
Divorced	1,197 (9)	1,022 (9)
Widowed	8,497 (64)	2,807 (24)
Cause of death: N (%)		
Ischaemic heart diseases	4,880 (37)	5,641 (48)
Myocardial infarction	1,342 (10)	1,906 (16)
Stroke	2,238 (17)	1,512 (13)
Haemorrhagic stroke	469 (4)	361 (3)
Ischaemic stroke	350 (3)	277 (2)
Heart failure	1,129 (8)	624 (5)
Blood pressure	1,745 (13)	983 (8)
Arrythmia	727 (5)	665 (6)

home locations for the year of death as calculated by Karipidis et al [Karipidis et al. 2014]. within the interdisciplinary SiRENE project.

Air pollution and meteorological exposure

We estimated nitrogen dioxide (NO_2), maximum temperature and precipitation data at home locations for all cases and control event dates (2 days averages). We used modelled daily NO_2 at 100 × 100 m spatial resolution, available from 2005 onwards for Switzerland [De Hoogh et al. 2019]. For the earlier years, we calculated individual NO_2 levels using routinely collected data from the nearest 'Immisionsdatenbank Luft (IDB)' (IDB Luft, Bern, Switzerland) combined with the annual mean observed in 2005. Modelled daily maximum temperature and precipitation were available at a 2 × 2 km

resolution for the whole of Switzerland for all 15 years of the study [MeteoSwiss 2017; MeteoSwiss 2016].

Statistical analyses

The association between average aircraft noise and cardiovascular mortality was estimated using conditional logistic regression [Janes, Sheppard, and Lumley 2005; Navidi 1998]. We used all primary cardiovascular causes of death as the primary outcome and created separate models for night-time (2 h exposure) and daytime deaths (overall night and four separate night-time exposure windows). We used the L_{Aeq} as primary exposure, modelled as a penalized spline with four degrees of freedom to reflect the shape of the association between acute aircraft noise exposure and mortality and adjusted for NO_2, maximum temperature, precipitation, and public holiday. We also computed separate models for the 2 h night-time noise exposure prior to death for three noise metrics (L_{Aeq}, L_{Amax}, and NAT_{55}) using categorical exposure variables to compute ORs for the noise exposure groups (10 dB exposure groups with reference at 20 and 40 dB for L_{Aeq} and L_{Amax}, respectively, and NAT_{55} 0; 1–2; 2–5; 6–15; >15 events) and calculated 'P for trend' values, as an indication for exposure-response relationships [Patino and Ferreira 2016]. We investigated possible modification in the association between night-time 2h-L_{Aeq} and mortality for individual characteristics and subgroups of the population. We reported the change in odds ratio (OR) per 10 dB increase 2h-L_{Aeq} with 95% confidence intervals. Finally, we calculated the population attributable fraction (PAF) for cardiovascular mortality based on the risks calculated in the 2h-L_{Aeq} categorical models [Perez and Künzli 2009] (Supplementary materials, Equation S1).

Results

We identified 24,886 adult deaths from cardiovascular cause between 2000 and 2015 within our study area in the vicinity of ZRH, of which 7,641 occurred during the night and 17,245 during the day (Table 5.1). The mean L_{Aeq} ranged from 17.6 to 45.2 dB for the different exposure time windows. On average, all three noise metrics were highest in the evening time window (19:00–23:00) and lowest in the core night (23:30–06:00). L_{Amax} was highly correlated with L_{Aeq} (Pearson correlation coefficient = 0.91, $P< 0.001$). A more detailed description of the aircraft noise exposure metrics can be found elsewhere [Saucy et al. 2020b].

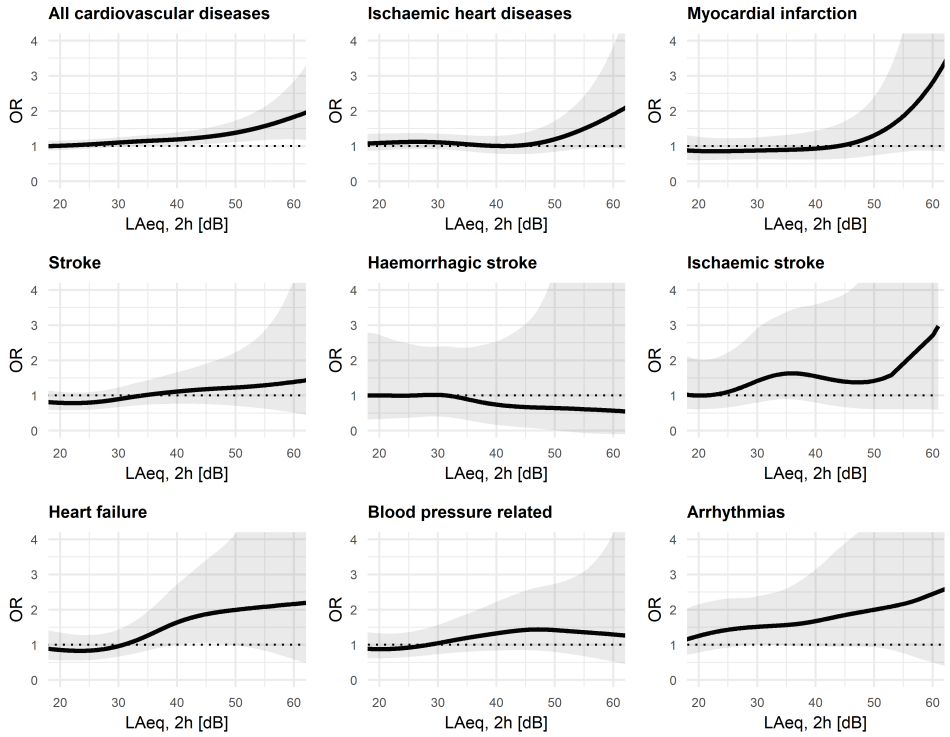

Figure 5.1: Odds of nighttime mortality in relation to 2h-L_{Aeq} levels.

We found an association between 2 h aircraft noise exposure preceding the time of a cardiovascular death during the night (Figure 5.1). Indication of an association was specifically observed for IHD, myocardial infarction, heart failure, and arrhythmias. The odds of nighttime cardiovascular mortality (all causes) was significantly increased for 2h-L_{Aeq} values above 40 dB with P for trend = 0.01 (Table 5.2). Linear exposure-response relationship was also significant for heart failure (P for trend = 0.05) and suggestive for IHD, without reaching significance (P = 0.18). We observed similar trends for 2h-L_{Amax} exposure as for 2h-L_{Aeq}. For 2h-NAT_{55}, we observed a significant increase in odds of mortality for heart failure for exposure values above five events within the 2 h window preceding death (Supplementary materials, Table S1). The odds of mortality were significantly stronger among females than males, especially for arrhythmias (Figure 5.2). Due to the limited number of observations for some diagnoses (e.g. haemorrhagic and ischaemic strokes), power was insufficient to make any statement about the shape of the exposure-response curve. Precision was generally lower for the highest exposure groups with fewer observations. Sensitivity analysis with additional adjustment for fine particles did not affect the results (Supplementary materials, Figure S4).

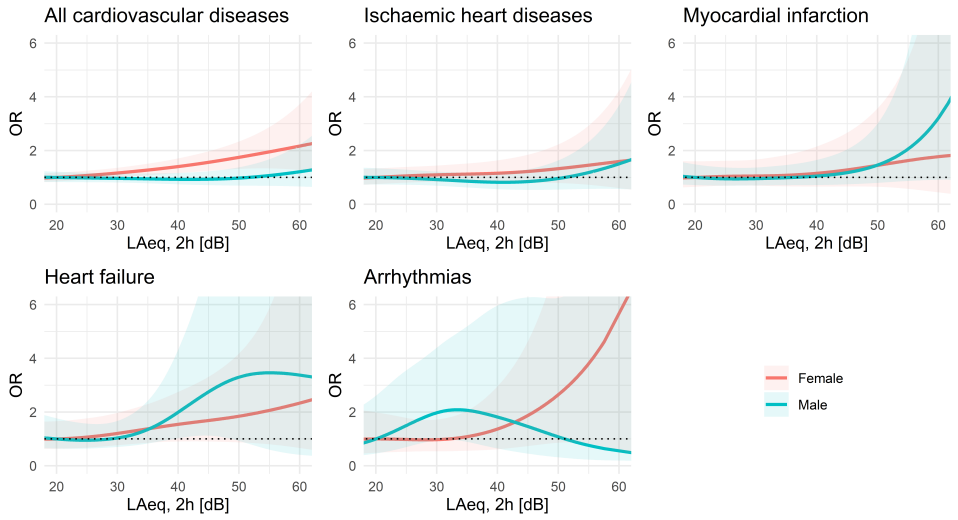

Figure 5.2: Odds of nighttime mortality in relation to 2h-L_{Aeq} levels, stratified by gender (reference = 20 dB).

Based on our findings presented in Table 5.2, and assuming a causal relationship, we estimated that 782 out of 24,886 deaths in our study population could be attributed to aircraft noise thus representing a PAF of 3%.

We found that the association between aircraft noise and nighttime cardiovascular deaths was significantly stronger for people living in quiet areas as compared to areas with higher night-time levels of road and railway noise and for people living in older buildings, most likely with less efficient sound insulation (Table 5.3). We observed a stronger association for females [OR= 1.13 (1.04–1.23)] than for males [OR = 0.98 (0.89–1.07)] and found a lower risk of mortality for Swiss as compared to men from the rest of Europe. The association between 2h-L_{Aeq} and mortality tended to be stronger with decreasing education level and socio-economic status, as well as older age. Finally, the association between 2h-L_{Aeq} and mortality was modified by civil status although not significant (P= 0.39), with the highest odds of mortality observed for divorced people, while being married showed the lowest risk of mortality for males, and was equally high as divorced for females. Graphical representations of these effect modifications are available in Supplementary materials, Figure S3.

For daytime deaths, no consistent risk increase was observed (Figure 5.3), although for arrhythmias, the morning exposure window (06:00– 07:00) could be critical (Supplementary materials, Figure S5).

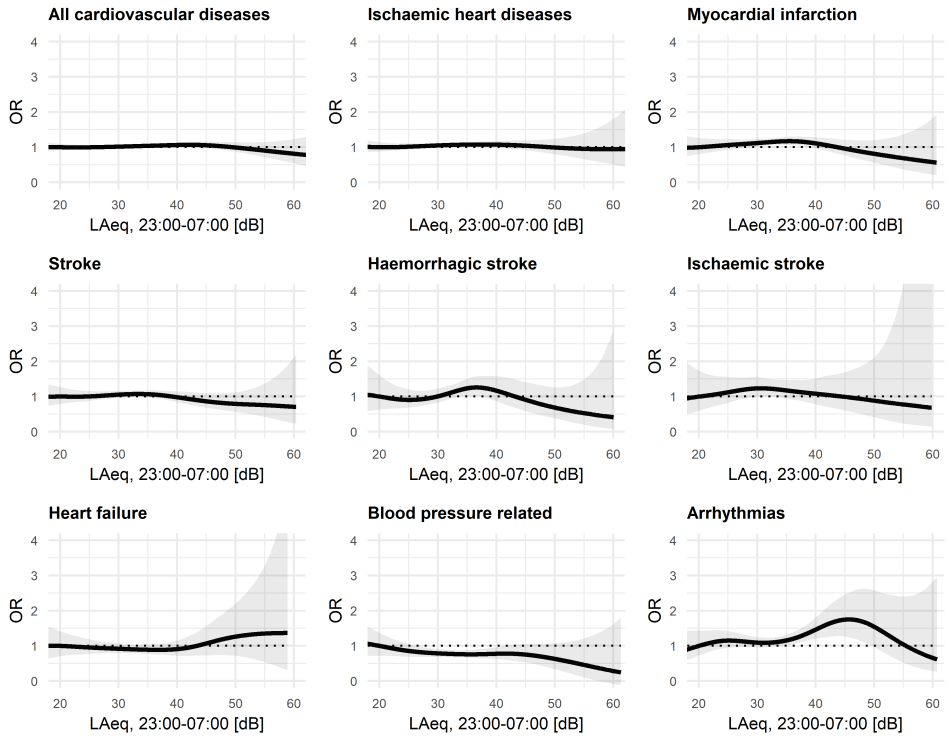

Figure 5.3: Odds of daytime mortality in relation to nighttime L_{Aeq} (23:00-07:00) levels of the preceding night.

Table 5.2: Associations between nighttime mortality from cardiovascular cause and noise exposure groups two hours preceding death (2h-L_{Aeq}). Statistically significant results at level *alpha*=5% are marked in bold, adjusted for NO_2, temperature, precipitation and holiday.

Exposure groups	All cardiovascular diseases			Ischaemic heart diseases			Myocardial infarction			Heart failure		
	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI
<20 dB	4245	1		1797	1		527	1		229	1	
20-30 dB	824	1.08	(0.92-1.26)	360	1.15	(0.90-1.47)	101	1.11	(0.67-1.79)	69	1.11	(0.63-1.99)
30-40 dB	1169	**1.23**	**(1.00-1.51)**	513	1.1	(0.80-1.51)	156	0.86	(0.45-1.64)	108	**2.08**	**(1.01-4.29)**
40-50 dB	1157	**1.33**	**(1.05-1.67)**	479	1.13	(0.78-1.64)	152	0.93	(0.46-1.88)	74	2.07	(0.93-4.61)
>50 dB	246	**1.44**	**(1.03-2.04)**	117	1.64	(0.96-2.79)	35	1.62	(0.62-4.25)	16	3.09	(0.94-10.23)
Trend	***P for trend = 0.01***			*P for trend = 0.18*			*P for trend = 0.57*			***P for trend = 0.05***		

Table 5.3: Effect modification of the association between 2h-L_{Aeq} and nighttime cardiovascular mortality, stratified by gender. Statistically significant results at level $\alpha = 5\%$ are marked in bold.

	All			Females*			Males		
covariates	cases	OR (95%CI)	p-int	cases	OR (95%CI)	p-int	cases	OR (95%CI)	p-int
Background noise			**0.01**			0.19			0.07
Low (tertile 1)	2683	**1.08 (1.02-1.15)**		1497	**1.15 (1.06-1.25)**		1186	1.00 (0.91-1.09)	
Middle (tertile 2)	2516	**1.06 (1.00-1.13)**		1337	**1.14 (1.04-1.24)**		1179	0.98 (0.90-1.08)	
High (tertile 3)	2442	1.04 (0.98-1.11)		1327	**1.11 (1.03-1.22)**		1115	0.96 (0.87-1.05)	
Building period			0.36			0.93			0.18
Before 1970	4607	**1.09 (1.01-1.18)**		2481	**1.14 (1.03-1.26)**		2126	1.05 (0.94-1.17)	
1970-1990	2243	1.04 (0.92-1.16)		1266	**1.16 (1.00-1.45)**		977	0.87 (0.73-1.05)	
After 1990	656	0.89 (0.71-1.12)		329	1.03 (0.74-1.43)		327	0.79 (0.57-1.09)	
Nationality			0.07			0.93			**0.01**
Swiss	6727	1.06 (0.99-1.12)		3759	**1.14 (1.05-1.24)**		2968	0.96 (0.87-1.06)	
Rest of Europe	415	**1.37 (1.06-1.78)**		161	1.11 (0.76-1.62)		254	**1.66 (1.14-2.41)**	
Other or unknown	499	0.90 (0.70-1.16)		241	1.07 (0.77-1.50)		258	0.74 (0.51-1.08)	
Education			0.36			0.77			0.27
Compulsory or less	2756	1.09 (0.99-1.20)		2085	**1.16 (1.04-1.29)**		671	0.94 (0.78-1.13)	
Upper secondary	3756	1.07 (0.98-1.17)		1814	1.09 (0.96-1.24)		1942	1.05 (0.93-1.19)	
Tertiary	949	0.91 (0.75-1.10)		153	1.43 (0.81, 2.52)		796	0.85 (0.69-1.05)	
SSEP**			0.81			0.76			0.72
Quintile 1 (lowest)	802	1.10 (0.93-131)		448	**1.24 (1.01-1.52)**		354	0.86 (0.63-1.16)	
Quintile 2	1115	1.10 (0.95-1.28)		630	**1.23 (1.01-1.51)**		485	0.96 (0.77-1.20)	
Quintile 3	1331	1.09 (0.95-1.27)		693	1.08 (0.88-1.33)		638	1.11 (0.91-1.36)	
Quintile 4	1907	1.07 (0.95-1.21)		1056	1.14 (0.97-1.34)		851	1.00 (0.83-1.20)	
Quintile 5 (highest)	2016	0.98 (0.87-1.11)		1007	1.04 (0.87-1.25)		1009	0.93 (0.79-1.10)	
Civil status			0.39			0.72			0.22
Married	2746	1.04 (0.94-1.15)		733	**1.22 (1.01-1.48)**		2013	0.98 (0.87-1.11)	
Widowed	3572	1.03 (0.95-1.13)		2691	1.10 (0.99-1.22)		881	0.87 (0.73-1.04)	
Single	660	1.14 (0.94-1.40)		374	1.16 (0.90-1.49)		286	1.13 (0.81-1.58)	
Divorced	663	**1.22 (1.00-1.51)**		363	1.22 (0.94-1.58)		300	1.25 (0.89-1.75)	
Age			0.71			0.79			0.82
<=65	664	1.02 (0.82-1.27)		170	1.07 (0.68-1.68)		494	1.00 (0.78-1.29)	
> 65	6977	**1.06 (1.00-1.13)**		3991	**1.14 (1.05-1.24)**		2986	0.97 (0.88-1.07)	

* The association between L_{Aeq} and all CVD mortality with stronger for females than for males (p-interaction = 0.02). ** SSEP: Swiss neighbourhood index of socioeconomic position.

Discussion

This study suggests that aircraft noise events during the night may trigger a cardiovascular death within two hours. The PAF estimate of 3% is comparable to other

triggers of cardiovascular mortality, such as anger, positive emotions, sexual activity, and heavy meals [Nawrot et al. 2011], and to previous estimates for long-term aircraft noise exposure [Correia et al. 2013].

To the best of our knowledge this is the first study investigating acute aircraft noise effects on mortality. Our current findings are broadly in line with our previous study investigating the association between long-term noise and cardiovascular mortality in Switzerland, which also found higher mortality for heart failure, myocardial infarction, and ischaemic stroke associated with aircraft noise and absence of associations for other cardiovascular causes of deaths [Héritier et al. 2017]. They also align with studies in other countries on long term health outcomes observed near airports [Weihofen et al. 2019; Hansell et al. 2013], and acute physiological responses to night-time aircraft noise. We used a spline to model the odds of mortality, without any a priori assumption on the shape of the association. During night and shorter time windows, we have observed higher day-to-day variation, which is most relevant for a case-crossover analysis. Except for arrhythmias and all CVD combined, where we observed steadily increasing exposure-response relationships with L_{Aeq}, the shape of the splines suggests a possible threshold in the range of 30–50 dB, which is rather low compared to studies on long-term night-time aircraft noise [European Environment Agency 2020; Vienneau et al. 2019]. However, these 2h-L_{Aeq} values might very well represent audible individual flight events when those occur during night-time exposure windows with only few flights per hour (Supplementary materials, Figure S6) [Locher et al. 2018].

We found suggestive evidence for effect modification by gender, nationality, civil status, and background transportation noise. Existing literature on gender differences and the effects of noise on health is rather inconsistent [Pyko et al. 2019; Vienneau et al. 2015]. Our study suggests a stronger risk of mortality among females for CVDs (all causes) but not for IHD, myocardial infarction, and heart failure. The gender difference observed in all causes of cardiovascular mortality is likely to be driven by a stronger association for arrhythmias, as well as a general older age at death among females. Pyko et al. suggested that higher risk of mortality among females may be due to possible higher susceptibility to stress response, as shown in higher salivary cortisol in response to noise exposure [Pyko et al. 2019]. The association between aircraft noise and mortality was more pronounced in areas with little railway and road traffic background noise. Single flight events are indeed more likely to be perceived and to cause potential physiological response in a quiet environment as compared to a noisy environment with possible noise

masking. We also observed higher effect size for people living in older buildings, where sound insulation is likely to be less efficient than in more recent constructions. This may explain part of the observed higher risk in people with lower socio-economic status usually living in less costly residential buildings. Our findings thus suggest that such social characteristics can affect the individual risk of mortality associated to aircraft noise exposure. Social inequities may therefore not only represent differences in environmental exposures levels as previously described [World Health Organization 2010] but also affect the risk of mortality from environmental factors.

A particular strength of this study is the high precision aircraft noise modelling accounting for single, specific flight events, yielding individual aircraft noise exposure estimates with high spatial and temporal accuracy for each death case. Nevertheless, some exposure misclassification is unavoidable, for instance due to inaccurate location (errors in the address history, residents not at home) or imprecision from the aircraft calculations (individual flights slightly deviating from the usual air routes). A strength of the case-crossover design is, however, that health risks are estimated based on the exposure difference between case and control events for the same person and the same location, thus minimizing bias from errors in exposure modelling. The choice of exposure time window can also be critical. In this study, we a priori considered a 2 h exposure window for nighttime deaths, as described for other triggers of cardiovascular mortality [Nawrot et al. 2011]. We cannot exclude that the time between first symptoms onset and death might exceed this delay in some cases, especially for patients dying in hospital or patients living alone with possible imprecision in time of death. The proportion of deaths occurring at home vs. in hospital is unknown in our study population, but evidence from other countries suggests that this number is rather limited [Dudas et al. 2011]. In both cases, misclassification is expected to be independent from exposure levels and health outcomes, resulting in an overall underestimation of the risk estimates.

Due to the night-time flight restriction in place at ZRH, the observed night-time aircraft noise levels were rather low. Further research should investigate if similar results can be reproduced in other locations, also including higher night-time exposure levels and individual sleeping patterns whenever available. We found only weak indication that night-time aircraft noise exposure (i.e. mainly early morning exposure), might also affect mortality occurring the next day. This may indicate that acute physiological reaction from aircraft noise is restricted to a few hours and does not persist into the following day. Longer averaged exposure intervals are also less susceptible to show important day-to-day

variations. Furthermore, we did not consider daytime noise exposure for the analysis of daytime deaths because we suspected substantial exposure misclassification when people are not at home during the day. Thus, future studies with appropriate design are needed to clarify whether aircraft noise during the day may also trigger cardiovascular deaths. Better understanding of the effects of noise characteristics and timing on health outcomes could have important implications on noise regulations, such as night-time road speed reduction or air traffic regulations [Griefahn, Marks, and Robens 2008].

Conclusions

Our findings suggest that night-time aircraft noise events may trigger cardiovascular deaths, which would explain 3% of all cases of death from cardiovascular cause in our population living in the vicinity of an international airport if this association was causal. Our study suggests that night-time aircraft noise exposure may be of particular importance in relation to IHD and heart failure, as also found for long-term exposures.

Data availability: The data underlying this article cannot be shared publicly due to the sensitivity of individual data used in the study. The data will be shared on reasonable request to the corresponding author.

Supplementary material: Supplementary material is available at European Heart Journal online `https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehaa957#supplementary-data`.

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Conflict of interest: The authors declare no conflict of interest.

Chapter 6

The role of extreme temperature in cause specific acute cardiovascular mortality in Switzerland: a case-crossover study

Apolline Saucy[1,2], Martina Ragettli[1,2], Beat Schäffer[3], Louise Tangermann[1,2], Danielle Vienneau[1,2], Kees de Hoogh[1,2], Jean-Marc Wunderli[3], Nicole Probst-Hensch[1,2], Martin Röösli[1,2]

[1] Swiss Tropical and Public Health Institute (Swiss TPH), Basel, Switzerland

[2] University of Basel, Basel, Switzerland

[3] Swiss Federal Laboratories for Materials Science and Technology (Empa), Dübendorf, Switzerland

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The role of extreme temperature in cause-specific acute cardiovascular mortality in Switzerland: A case-crossover study

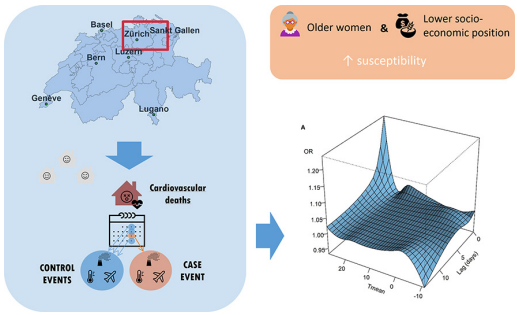
Apolline Saucy [a,b], Martina S. Ragettli [a,b], Danielle Vienneau [a,b], Kees de Hoogh [a,b], Louise Tangermann [a,b], Beat Schäffer [c], Jean-Marc Wunderli [c], Nicole Probst-Hensch [a,b], Martin Röösli [a,b,*]

[a] Swiss Tropical and Public Health Institute (SwissTPH), Basel, Switzerland
[b] University of Basel, Basel, Switzerland
[c] Empa, Swiss Federal Laboratories for Materials Science and Technology, Dübendorf, Switzerland

HIGHLIGHTS

- Temperature related risk of cardiovascular mortality was highest on hot days.
- 2% of deaths were attributable to hot temperature and 5% to cold temperature.
- Older women with lower socio-economic position are more vulnerable to heat.
- Housing and air pollution, but not noise, modify vulnerability to temperature.
- Understanding effect modifiers is relevant for preventing temperature-related mortality.

GRAPHICAL ABSTRACT



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ABSTRACT

Since the 2003 heatwave in Europe, evidence has been rapidly increasing on the association between extreme temperature and all-cause mortality. Little is known, however, about cause-specific cardiovascular mortality, effect modification by air pollution and aircraft noise, and which population groups are the most vulnerable to extreme temperature. We conducted a time-stratified case-crossover study in Zurich, Switzerland, including all adult cardiovascular deaths between 2000 and 2015 with precise individual exposure estimates at home location. We estimated the risk of 24,884 cardiovascular deaths associated with heat and cold using distributed non-linear lag models. We investigated potential effect modification of temperature-related mortality by fine particles, nitrogen dioxide, and night-time aircraft noise and performed stratified analyses across individual and social characteristics. We found increased risk of mortality for heat (odds ratio OR = 1.28 [95% confidence interval: 1.11–1.49] for 99th percentile of daily Tmean (24 °C) versus optimum temperature at 20 °C) and cold (OR = 1.15 [0.95–1.39], 5th percentile of daily Tmean (−3 °C) versus optimum temperature at 20 °C). Heat-related mortality was particularly strong for myocardial infarctions and hypertension related deaths, and among older women (>75 years). Analysis of effect modification also indicated that older women with lower socio-economic position and education are at higher risk for heat-related mortality. $PM_{2.5}$ increased the risk of heat-related mortality for heart failure, but not all-cause cardiovascular mortality. This study provides useful information for preventing cause-specific cardiovascular temperature-related mortality in moderate climate zones comparable to Switzerland.

* Corresponding author at: Socinstrasse 57, 4051 Basel, Switzerland.
E-mail address: martin.roosli@swisstph.ch (M. Röösli).

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Abstract

Since the 2003 heatwave in Europe, evidence has been rapidly increasing on the association between extreme temperature and all-cause mortality. Little is known, however, about cause-specific cardiovascular mortality, effect modification by air pollution and aircraft noise, and which population groups are the most vulnerable to extreme temperature. We conducted a time-stratified case-crossover study in Zurich, Switzerland, including all adult cardiovascular deaths between 2000 and 2015 with precise individual exposure estimates at home location. We estimated the risk of 24,884 cardiovascular deaths associated with heat and cold using distributed non-linear lag models. We investigated potential effect modification of temperature-related mortality by fine particles, nitrogen dioxide, and night-time aircraft noise and performed stratified analyses across individual and social characteristics. We found increased risk of mortality for heat (odds ratio OR = 1.28 [95% confidence interval: 1.11–1.49] for 99$^{\text{th}}$ percentile of daily Tmean (24 °C) versus optimum temperature at 20 °C) and cold (OR = 1.15 [0.95–1.39], 5$^{\text{th}}$ percentile of daily Tmean (-3 °C) versus optimum temperature at 20 °C). Heat-related mortality was particularly strong for myocardial infarctions and hypertension related deaths, and among older women (>75 years). Analysis of effect modification also indicated that older women with lower socioeconomic position and education are at higher risk for heat-related mortality. $PM_{2.5}$ increased the risk of heat-related mortality for heart failure, but not all-cause cardiovascular mortality. This study provides useful information for preventing cause-specific cardiovascular temperature-related mortality in moderate climate zones comparable to Switzerland.

Introduction

There is well-established evidence of the association between heat and cold and mortality from a range of countries and climatic regions around the world [Gasparrini et al. 2015; Arbuthnott et al. 2020; Ryti, Guo, and Jaakkola 2016; Breitner et al. 2014]. In the context of a changing climate, the increased mortality observed during recent heatwaves has increasingly raised public health concern [Ragettli et al. 2017; Watts et al. 2020; Federal Office for the Environment 2020a]. It is estimated that the heatwave of 2003 caused about 70,000 excess deaths in Europe [Robine et al. 2008]. Since this notable episode, several further heatwaves have occurred across Europe leading to further deaths [Barriopedro et al. 2011; European Environment Agency 2021]. In Switzerland,

the excess mortality was estimated around 1'000 for 2003 [Grize et al. 2005], 800 for 2015 [Vicedo-Cabrera et al. 2016], 200 in 2018, and 500 in 2019 [Ragettli and Röösli 2021]. It is expected that most countries will experience more heatwave events in the future, especially in urban settings [Field et al. 2014]. Cold temperatures are also associated with an important burden of disease in many countries, associated with even higher attributable risk fractions than heat [Oudin Åström et al. 2018]. The shape of the association between temperature and mortality, as well as optimum temperature, varies between areas [Gasparrini et al. 2015].

Cardiovascular diseases are among the leading causes of temperature-related mortality [Iñiguez, Royé, and Tobías 2020]. Disparate exposure-response functions for cardiovascular diseases may be the consequence of different underlying physiological mechanisms; however, this is yet to be elucidated because few studies have systematically investigated the effects of temperature on cause-specific cardiovascular mortality. For instance, a recent longitudinal study reported a clear increased risk of cerebrovascular mortality in Lisbon for both warm (relative risk RR = 1.65 [1.37, 1.98] for the 99^{th} percentile) and cold temperatures (RR = 2.09 [1.74, 2.51] for the 1^{st} percentile) [Rodrigues, Santana, and Rocha 2019].

Little is also known about effect modification of temperature-related cardiovascular mortality, since most papers on this topic have focussed on all-cause mortality. Son et al. conducted a meta-analysis on all-cause temperature-related mortality using evidence from around the world published before 2017, reporting increased relative risks of mortality for women with heat and for older individuals with both heat and cold [Son, Liu, and Bell 2019]. Their meta-analysis suggested limited evidence of effect modification by individual characteristics such as education, civil status and socio-economic position and weak evidence for effect modification by air pollution (ozone and PM_{10}). More recently, studies further investigated the role of age, gender and socio-economic position on temperature-related mortality. Marí-Dell'Olmo and colleagues observed consistently increased risk of heat-related mortality among women and the older population in Spain. They also reported effect modification by education in men, with lower education, while women were similarly affected throughout all education groups [Marí-Dell'Olmo et al. 2019]. In contrast, the role of air pollution in temperature-related mortality is less clear. Analitis and colleagues investigated the effect modification of temperature-related mortality by air pollution, reporting an increase in heat-related cardiovascular mortality with higher levels of ozone and PM_{10}, but only for some age groups and diagnoses. They did

not find any effect modification by NO_2 [Analitis et al. 2018]. More research is needed to further understand the relation between extreme temperatures and cause-specific mortality, and how those relate to particularly vulnerable populations [Benmarhnia et al. 2015]. A better understanding of the synergistic effects of temperature, air pollution among different groups of the population is a key to promote equitable health in future urbanization and temperature-mortality mitigation efforts.

The aim of this study was to investigate the role of extreme temperature on cause-specific cardiovascular mortality using a case-crossover study design, and to identify the groups (in this study population of mortality cases) most vulnerable to heat and cold. Much of the research to date on temperature-related mortality uses time-series designs with one or several central temperature monitoring station(s) for exposure assessment, ignoring the spatial contrasts in temperature across the study area [Benmarhnia et al. 2015]. The advantage of the case-crossover approach used in this study is that it exploits fine scale spatio-temporal temperature data, thus reducing the risk of exposure misclassification. By minimizing confounding from individual characteristics, the case-crossover design also strengthens effect modification analyses aimed to identify the most vulnerable groups of the population. This study specifically leveraged a large and precise environmental exposure database created for a previous study investigating the acute cardiovascular effects of aircraft noise around Zurich Airport in Switzerland based on the Swiss National Cohort (SNC) [Saucy et al. 2020a]. The integrated database enabled the investigation of potential interaction of temperature with air pollution and, for the first time, acute noise exposure.

Methods

Study population

The SNC is a long-term cohort based on linkage of national census and mortality records for the whole Swiss population, containing personal information such as age, sex, socio-economic position, address history and mortality information (cause, date and time of death) [Spoerri et al. 2010]. With a large range of individual information, including a Swiss-specific indicator for neighbourhood-based socio-economic position, the SNC provides longitudinal data suitable for investigating the health effects associated with differences in socio-economic profiles [Bopp et al. 2009]. The selection of the study

population was motivated by a previous study investigating the acute cardiovascular effects of aircraft noise in the vicinity of Zurich Airport which adjusted for air pollution and temperature effects. In leveraging this database, we now specifically focus on the short term effects of temperature in relation to mortality. Thus, we selected 24,886 cases of cardiovascular death occurring between 2000 and 2015 in adults >30 years, with available address at time of death and exposed to levels of aircraft noise above 47 dB during the day and/or 37 dB during the night [Schäffer et al. 2012] (Supplementary Figure A.1). This study area includes urban, peri-urban, and rural areas (Table 6.1). We considered the following primary causes of death: all cardiovascular diseases (CVD) (ICD-10: I00-I99), ischaemic heart diseases (ICD-10: I20-I25), myocardial infarction (ICD-10: I21-I22), stroke (ICD-10: I60-I64), heart failure (ICD-10: I50), hypertensive diseases (ICD-10: I10-I15), and arrhythmias (ICD-10: I44-I49).

Study design

We used a case-crossover study design to investigate the acute effects of heat and cold on cardiovascular mortality. The case-crossover study design, first described by Maclure in 1992, is a case-only approach, where each case event is matched with several control events for the same person at different times [Maclure 1991]. Each case was matched with up to four control events, selected within the same month and matched on day of the week, following a time-stratified sampling scheme [Navidi 1998]. As opposed to time-series where temperature is assigned from a central monitoring station, this design allowed us to use precise individual daily temperature estimates incorporating spatial contrasts in addition to the temporal.

Exposure assessment

We assigned daily outdoor temperature values at the home location for each of the case and control event days. We used 2 km resolution historical meteorological exposure maps from MeteoSwiss (Grid-Data Products), including daily maximum (Tmax), minimum (Tmin) and mean (Tmean) temperature and precipitation. Temperature estimates in these maps were calculated at 2 m above ground level, using near-surface air temperature measurements following a deterministic analysis method specifically designed for temperature interpolation in mountainous areas [MeteoSwiss 2017; MeteoSwiss 2016].

Table 6.1: Summary statistics of the characteristics of all deaths included in the study with respect to the temperature distribution on the day of death.

	N (%)	Tmean [°C]			Tmin [°C]			Tmax [°C]		
Percentiles		**5th**	**90th**	**99th**	**5th**	**90th**	**99th**	**5th**	**90th**	**99th**
Cause of death										
All-cause cardiovascular	24886 (100)	-2.76	19.37	24.59	-5.68	14.17	17.72	-0.28	25.79	32.81
Ischaemic heart diseases	10521 (41)	-2.97	19.53	24.61	-5.81	14.22	17.67	-0.26	26.04	32.96
Myocardial infarction	3248 (13)	-2.83	19.23	24.95	-5.80	14.21	17.80	-0.25	25.66	32.99
Stroke	3750 (15)	-2.44	19.23	24.45	-5.54	14.06	17.72	-0.07	25.66	32.66
Heart failure	1753 (7)	-3.04	18.92	25.16	-6.02	13.89	18.02	-0.49	25.22	32.85
Hypertensive diseases	2728 (11)	-2.56	19.27	24.52	-5.59	14.06	17.75	-0.30	25.55	32.67
Arrhythmias	1392 (6)	-2.84	19.50	24.56	-5.44	14.26	17.65	-0.51	26.07	32.80
Gender										
Female	13269 (53)	-2.74	19.29	24.45	-5.65	14.15	17.67	-0.28	25.70	32.62
Male	11617 (47)	-2.79	19.44	24.80	-5.68	14.21	17.77	-0.28	25.93	32.94
Age groups										
<= 75	5632 (23)	-2.96	19.26	24.83	-5.98	14.20	17.75	-0.48	25.72	32.93
75-85	8324 (33)	-2.45	19.56	24.72	-5.32	14.22	17.70	-0.14	26.03	33.14
>85	10930 (44)	-2.71	19.34	24.50	-5.62	14.12	17.70	-0.19	25.70	32.56
*Socio-economic position**										
1	2512 (10)	-2.70	19.59	24.78	-5.67	14.24	17.64	-0.26	26.03	32.97
2	3685 (15)	-2.89	19.17	24.53	-5.85	14.02	17.76	-0.39	25.49	32.95
3	4470 (18)	-2.87	19.31	24.80	-5.83	14.15	17.68	-0.40	25.66	32.91
4	6263 (25)	-2.73	19.52	24.54	-5.60	14.16	17.72	-0.26	26.09	32.62
5	6572 (26)	-2.64	19.26	24.87	-5.53	14.27	17.78	-0.15	25.68	32.95
Unknown	1384 (6)	-2.83	19.15	24.08	-5.53	14.14	17.61	-0.68	25.52	31.47
Education										
Compulsory or less	8830 (35)	-2.94	19.32	24.52	-5.70	14.16	17.76	-0.49	25.84	32.60
Upper secondary level	12353 (50)	-2.71	19.38	24.62	-5.63	14.16	17.69	-0.15	25.83	32.86
Tertiary level	3150 (13)	-2.74	19.50	24.61	-5.77	14.30	17.71	-0.28	25.80	32.94
Unknown	553 (2)	-2.06	18.64	24.61	-5.46	13.41	18.04	0.42	24.86	32.57
Urbanisation										
urban	9108 (36)	-2.74	19.51	24.44	-5.80	14.27	17.81	-0.31	25.89	32.46
peri-urban	14347 (58)	-2.80	19.34	24.68	-5.56	14.16	17.67	-0.25	25.78	33.01
rural	1431 (6)	-2.70	18.73	24.43	-5.48	13.72	17.45	-0.27	25.10	32.50
Building period										
before 1970	9478	-2.67	19.36	24.59	-5.55	14.19	17.67	-0.07	25.79	32.78
1970-1990	8631	-2.93	19.29	24.45	-5.79	14.11	17.59	-0.48	25.87	33.70
after 1990	6302	-2.63	19.42	24.85	-6.61	14.20	17.81	-0.22	25.81	32.92
Unknown	475 (2)	-3.57	19.27	25.07	-6.66	14.14	18.25	-1.44	25.16	32.95
Civil status										
Married	9286 (37)	-2.54	19.61	24.64	-5.56	14.34	17.78	-0.01	26.14	33.03
Non married	15600 (63)	-2.85	19.20	24.55	-5.70	14.06	17.69	-0.44	25.55	32.71

* Socio-economic position index ranging from lowest (0) to highest (5) quantiles [Panczak et al. 2012].

We used 4-day average fine particles ($PM_{2.5}$) and nitrogen dioxide (NO_2) exposure data at home location. Daily $PM_{2.5}$ and NO_2 were available at 100 m resolution for Switzerland, from 2003 to 2013 and 2005 to 2015 respectively [De Hoogh et al. 2019;

De Hoogh et al. 2018]. To obtain individual $PM_{2.5}$ data for the years 2014 and 2015, we extended the existing models to these years at 100 × 100 m resolution following the 4-stage modelling approach described by [De Hoogh et al. 2018]. To extend the time series to include previous years (2000 to 2002 and 2000 to 2004 respectively), we estimated daily $PM_{2.5}$ and NO_2 exposure at the place of event using the spatial distribution of the annual averages at home location for the first available modelled year calibrated by the daily values from routinely collected data in Dübendorf, located in the centre of the study area following a two-stage modelling approach (Supplementary Figure A.2).

Aircraft noise was calculated at home locations by combining a list of all aircraft movements at Zurich airport between 2000 and 2015 with outdoor aircraft noise exposure calculations at 250 × 250 m resolution, specific for aircraft type, air route, time, and year as previously described in detail [Saucy et al. 2020b]. We used the average noise exposure during the night preceding daytime deaths and the average noise exposure within 2h preceding the night-time deaths. To make these comparable, we normalized the two types of noise exposure values before aggregating the corresponding z-values into a single exposure measure. Other sources of transportation noise (e.g. road traffic and railway noise) were not considered in this analysis. Noise from road traffic and railways typically show little day-to-day variability and are therefore already adjusted by the individual matching in the case-crossover study design. This is the first study to investigate whether aircraft noise, which has a high day-to-day variation, is a confounder in the short-term association between temperature and cardiovascular mortality.

Statistical analyses

We investigated the association between cardiovascular mortality and temperature using a distributed lag non-linear model (DLNM) approach, as described by Gasparrini et al. [Gasparrini 2014]. The DLNM approach relies on the definition of a "cross-basis" function, allowing for non-linear and delayed effect of temperature [Goldberg et al. 2011]. We modelled the relationship between daily average temperature (Tmean) and mortality using a lag structure up to 14 days before death. The lag function was specified as a natural spline with two equally spaced knots on the logarithmic scale and Tmean as a b-spline with three knots placed at the 10^{th}, 75^{th} and 90^{th} percentiles of the annual temperature distribution. The choice of the temperature knots was defined a-priori as described in other studies [Gasparrini et al. 2015; Iñiguez, Royé, and Tobías 2020] and validated using Akaike's criterion (AIC). For air pollution adjustment, 2 to 5 days

averages were tested and selected by minimizing the AIC. We conducted conditional logistic regression adjusted for 2-days average precipitation, 4-days average NO_2 and/or $PM_{2.5}$, normalized aircraft noise prior to deaths, and national holidays. We estimated the odds ratio (OR) of mortality as the deviation from the empirically derived optimum temperature (20°C) to the 99^{th} percentile of the annual Tmean distribution for heat and from the optimum temperature to the 5^{th} percentile for cold as described by Gasparrini et al. [Gasparrini and Leone 2014]. The reference value at 20°C is derived from an estimate of the optimum temperature previously calculated for Switzerland [Vicedo-Cabrera et al. 2018a] and corresponds approximately to the 90^{th} percentile of the daily Tmean distribution in our data. As heat-related health effects usually last up to a week [Ragettli et al. 2017], and to account for potential short-term harvesting, we reported cumulative OR over lags 0–7 for heat-related mortality. For cold-related mortality, cumulative OR include lags 0 to 14 to consider the longer delay for cold related mortality. We ran sensitivity analyses with 21 days lags to account for potential harvesting effect for cold temperatures, as well as separate analysis using Tmin and Tmax instead of Tmean as main exposure metrics. To investigate the effect modification by non-varying individual characteristics, we conducted stratified analyses based on potential high vulnerability groups such as sex, age, building period, socio-economic status, education, and marital status.

The fraction of mortality cases attributable to heat and cold was estimated by combining the temperature-mortality function derived for Tmin and Tmax with the distribution of observed temperature (in 5°C temperature classes) and the observed average number of deaths per day.

A number of additional models were conducted. We assessed the potential effect modification of heat-related cardiovascular mortality with short-term ambient air pollution and aircraft noise—other acute triggers of cardiovascular mortality—by introducing an interaction term. As heat effects are found to last up to 3 to 5 days [Ragettli et al. 2017; Analitis et al. 2018], we investigated the effect modification by 4-day average air pollution levels on the association between heat (Tmean averaged for lags 0–3) and cardiovascular mortality. We modelled Tmean as a second-degree polynomial term and introduced interaction terms with NO_2, $PM_{2.5}$, and normalized aircraft noise. We created separate models for each pollutant and specific cause of death. All models were fully adjusted for all other exposures (Supplementary Equation A.1). We report the change

in the OR of heat and cold related mortality for increasing levels of 4-days average air pollution and aircraft noise in the night preceding death respectively.

Results

Tmean ranged between -14 and +28 °C (mean = 9°C) within the study population. Tmean was highly correlated with Tmin (0.84) and with Tmax (0.95, Pearson correlation coefficient). The temperature distribution was homogeneous between the different groups of the population presented in Table 6.1. More cases of death from cardiovascular origin were observed during the summer than winter (Supplementary Figure A.3). The OR of cardiovascular mortality associated with Tmean are represented in Figure 6.1. For heat effects, the OR of the 99th percentile of the annual temperature distribution (24°C) compared to the 90th percentile (20°C) was 1.28 (95% CI =1.11-1.49), and the corresponding OR for the 5th percentile (-3°C) was 1.15 (95% CI = 0.95-1.39) for cold effects (Table 6.2). The shape of the association between annual temperature and cardiovascular mortality was similar across all temperature metrics (Tmin, Tmean, Tmax), with an increase in the OR of mortality observed from 15°C for Tmin and 27°C for Tmax (Supplementary Figure A.4). The increased OR of mortality lasted up to 5 days for heat and over 14 days for cold (Figure 6.1). Sensitivity analyses extending the lag period to 21 days to account for potential harvesting effect did not affect these findings. The estimated mortality fraction attributable to higher temperatures (above the optimum temperature at 20 °C) was 2% and to colder temperatures (below the optimum temperature) 5%.

With respect to heat related mortality, strongest associations were found for hypertension related deaths and myocardial infarction (Table 6.2), and the risk of mortality was higher for women than men (41% increase in OR of cardiovascular mortality for women versus 14% for men). We also observed increased risk of mortality for older individuals and for those with less education, living in older buildings, and who were not married. In general, cold temperatures were not significantly associated with mortality, although significantly increased ORs were observed individuals with low socio-economic position, low education and not married.

In general, heat-related effects were stronger in women with lower socio-economic position and lower education (Table A.1). In men, the stronger heat-related effects were

in those with higher socio-economic position, which has driven the corresponding result in the full sample (Table 6.2).

We did not observe strong indications of effect modification from $PM_{2.5}$ and NO_2 in relation to heat or cold for all cause cardiovascular mortality (Figure 6.2). However, heat-related heart failure mortality increased with increasing $PM_{2.5}$ (p-value of interaction term = 0.03). The same tendency was observed for NO_2, although not significant (p-interaction = 0.86). The OR of cold-related mortality for myocardial infarction was slightly increased at higher levels of NO_2 without reaching significance

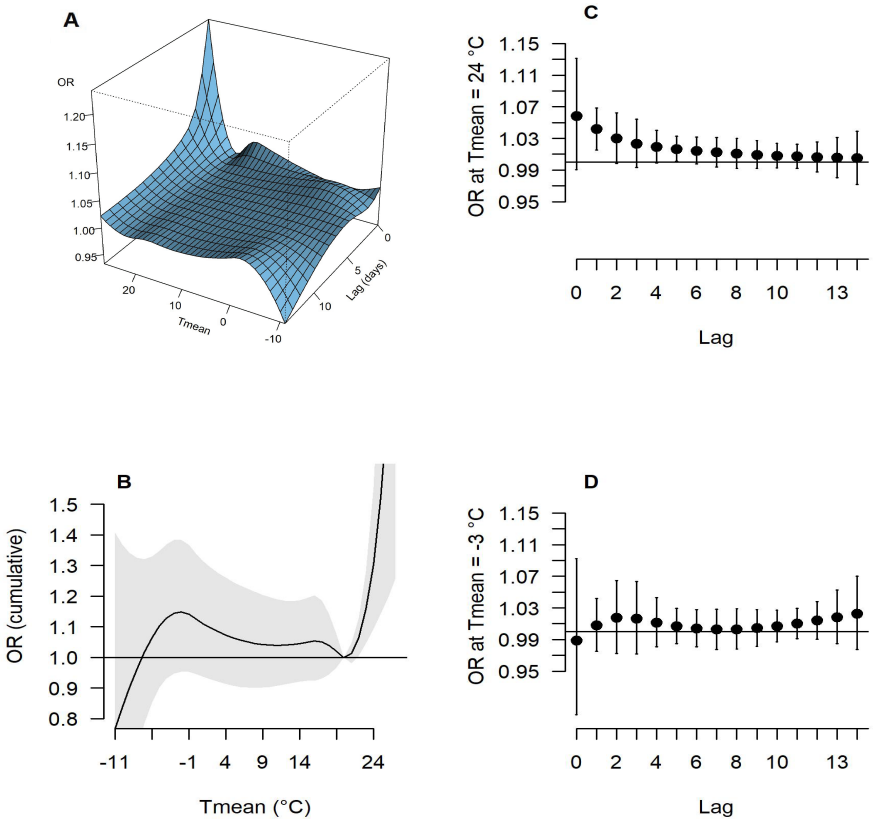

Figure 6.1: Odds ratios (ORs) of mortality associated with annual mean absolute temperature (Tabs). A) shows the mortality response function for annual Tmean and lag days 0 to 14; B) shows the ORs for daily Tmean cumulative over lag 0 to 14 days; C) shows the ORs of mortality for various lags between 0 to 14 days for heat (99^{th} percentile of the annual Tmean temperature distribution); D) shows the ORs of mortality for various lags between 0 to 14 days for cold (5^{th} percentile of the annual Tmean temperature distribution).

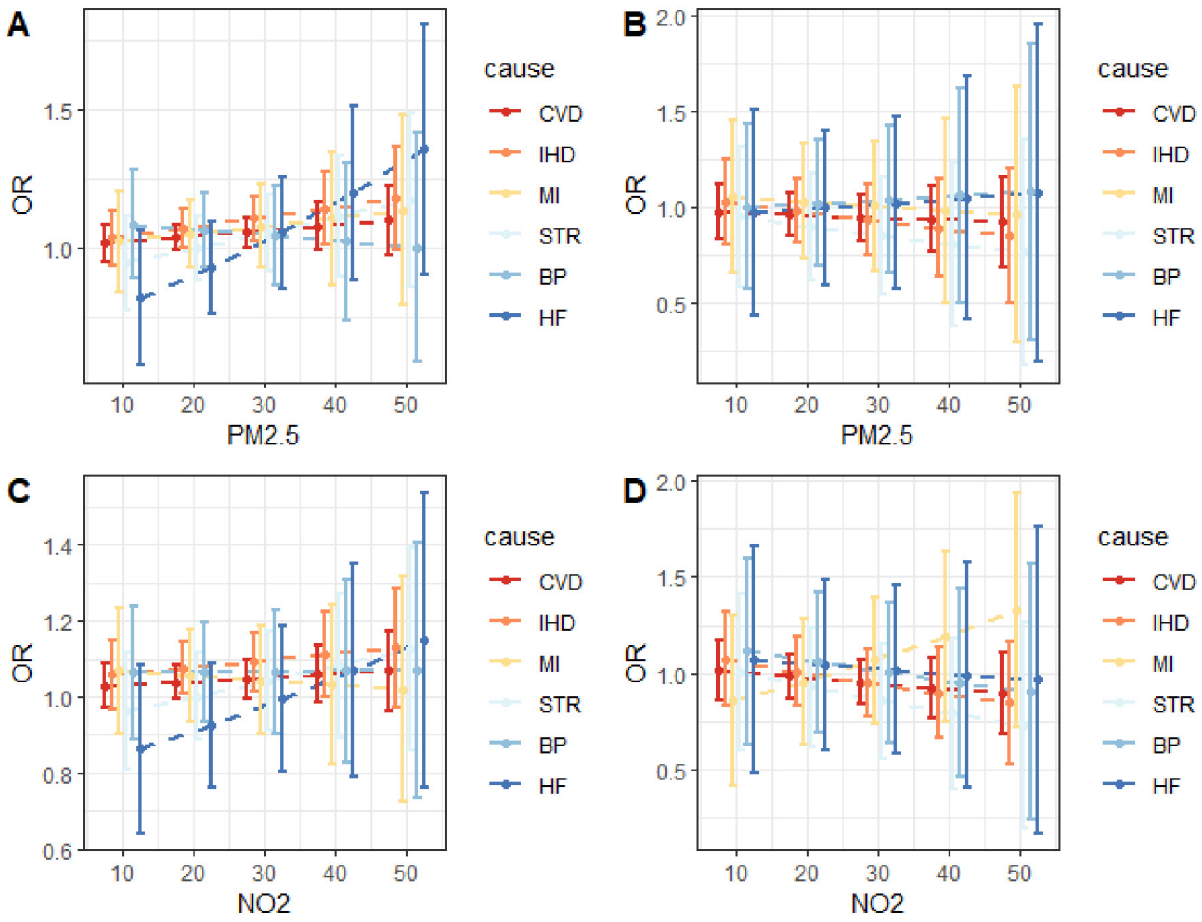

Figure 6.2: Odds ratio (OR) of temperature-related cardiovascular mortality associated with increasing NO_2 and $PM_{2.5}$ levels based on the interaction models. The left panes (A and C) present heat-related mortality (90^{th} to 99^{th} percentile of the annual distribution of Tmean averaged over lags 0–3). The right panes (B and D) present cold-related mortality (90^{th} to 5^{th} percentile of the annual distribution of Tmean averaged over lags 0–3). The ORs are displayed for all cardiovascular diseases (CVD), ischaemic heart diseases (IHD), myocardial infarction (MI), stroke (STR), hypertensive diseases (BP), and heart failure (HF).

(p-interaction = 0.50) (Figure 6.2). We found no evidence of an interaction with acute aircraft noise.

Discussion

This is one of the first studies investigating the temperature-related mortality for cause-specific cardiovascular mortality. We found increased odds of mortality mainly for heat but also in tendency for cold in our study population. The strongest asso-

Table 6.2: OR of cardiovascular mortality for heat and cold in relation to optimum temperature at 20°C, stratified over individual characteristics, cumulative over 0–7 lag days for heat and over 0–14 lags for cold. Statistically significant results (α=5%) are marked in bold.

Groups	n	OR heat (p.99)*	OR cold (p.5)*
All	24886	**1.28 (1.11-1.49)**	1.15 (0.95-1.39)
Diagnosis			
Ischaemic Heart Disease	10521	**1.30 (1.04-1.62)**	1.07 (0.80-1.43)
Myocardial infarction	3248	**1.67 (1.09-2.55)**	1.00 (0.59-1.72)
Stroke	3750	1.37 (0.94-2.00)	0.95 (0.59-1.54)
Heart failure	1753	0.98 (0.57-1.68)	1.75 (0.88-3.49)
Hypertensive diseases	2728	**1.91 (1.20-3.06)**	1.49 (0.83-2.66)
Arrhythmias	1392	1.25 (0.68-2.28)	1.54 (0.68-3.46)
Sex			
men	11617	1.14 (0.92-1.42)	1.17 (0.89-1.54)
women	13269	**1.41 (1.16-1.72)**	1.14 (0.88-1.47)
Age groups			
<75	5632	1.11 (0.82-1.50)	0.89 (0.60-1.32)
75-85	7667	**1.48 (1.15-1.91)**	1.33 (0.94-1.86)
>85	12079	**1.28 (1.04-1.59)**	1.15 (0.88-1.52)
Building period			
Before 1970	14957	**1.29 (1.07-1.56)**	1.19 (0.94-1.52)
1970-1990	7082	1.24 (0.94-1.62)	1.00 (0.70-1.43)
After 1990	2372	1.19 (0.71-1.97)	1.12 (0.58-2.17)
Socio-economic status			
Low (1st tertile)	8106	1.20 (0.92-1.55)	**1.38 (1.00-1.92)**
Middle (2nd tertile)	23502	**1.29 (1.11-1.50)**	1.14 (0.94-1.39)
High (3rd tertile)	7666	**1.38 (1.07-1.80)**	0.85 (0.60-1.20)
Education			
Compulsory or less	8830	**1.49 (1.17-1.91)**	**1.37 (1.00-1.88)**
Upper secondary	12353	**1.25 (1.02-1.55)**	1.08 (0.83-1.41)
Tertiary	3150	0.97 (0.65-1.45)	0.77 (0.45-1.32)
Civil status			
Married	9286	1.10 (0.87-1.38)	0.98 (0.72-1.33)
Non-married	15600	**1.44 (1.19-1.74)**	**1.27 (1.00-1.61)**

* Adjusted for precipitation, NO_2, $PM_{2.5}$, normalizedL_{Aeq}, national holidays, and firework days.

ciations with heat were found for ischaemic heart diseases, myocardial infarction, and hypertension-related causes of deaths. Further, our analysis suggests that older women with lower socio-economic position and lower education are at higher risk for heat-related mortality. We did not find a strong interaction between air pollutants and temperature-related mortality, except for heat-related heart failure and $PM_{2.5}$.

The shape of the association between temperature and mortality in the Zurich region is similar to observations in cities like Stockholm or Toronto with similar optimum temperature around 20°C [Gasparrini et al. 2015]. While the OR of mortality steadily increases with maximum temperature, the increase in risk with cold temperature was modest with little evidence for a risk increase in the most extreme cold temperature range. The lowest temperatures observed in this study are likely to be in the more rural areas and at higher altitude which are colder over the whole year. We expect this population is either better equipped (e.g. efficient insulation and heating system) or adapted for cold weather, possibly explaining this pattern. It may also be that the design using a one week interval between case and control events may be less suitable for cold compared to heat, specifically given that the effects of very cold temperatures are known to last over a longer period [Gasparrini et al. 2015]

Having modest odds ratios for moderate to cold temperature does not necessarily mean that attributable fraction is also small. In many cities around the world, moderate cold temperatures are common and, similar to our study, the highest temperature-related mortality burden has been attributed to the contribution of moderate cold [Gasparrini et al. 2015; Fu et al. 2018]

We found that heat-related mortality was especially driven by ischaemic heart disease including myocardial infarction (1.67 [1.09-2.55]) and by hypertensive diseases (1.91 [1.20-3.06]). In addition to respiratory diseases, [Gasparrini et al. 2012] also reported increased mortality for myocardial infarctions, arrhythmias and pulmonary heart diseases. Contrary to previous research in Lisbon, we did not find evidence of cold-related mortality for cerebrovascular diseases [Rodrigues, Santana, and Rocha 2019]. Increased heart rate and organ oxygen demand resulting from general vasodilatation required for body temperature regulation during heat events can explain the occurrence of ischaemic events. Heat-related heart failure seems to occur in combination with fine particles, possibly as a sign of cardiac exhaustion after combined stress events. While the increase in hypertension-related mortality may seem contradictory as a response to heat, our results are coherent with recent research also showing an increased risk of mortality for people diagnosed with hypertension. In parallel, they observed a reduction in the number of hospitalization due to acute hypertensive disease during heatwaves [Ragettli, Schulte, and Röösli 2021]. These two opposite effects were attributed to a possible interaction between heat and anti-hypertensive medication, which may explain our similar findings. For cold temperature, the increased cardiovascular mortality was driven by heart failure

and hypertension related deaths. Even though this was not significant in our sample, it is compatible with the physiological response to cold temperatures through general vasoconstriction and increased peripheral resistance.

For cardiovascular deaths specifically, studies to date mainly report that ozone and $PM_{2.5}$ modify the association between temperature and mortality, and only few studies included interaction with NO_2 [Analitis et al. 2018]. We found that fine particles modified the association between heat and mortality due to heart failure, but not other cardiovascular deaths. NO_2 did not interact with temperature-related mortality. We did not find clear evidence for an interaction between heat and aircraft noise, as could be expected due to more frequent open windows during warm nights.

Our effect modification analysis showed that less privileged groups of the population were at higher risk for temperature-related mortality. Namely, the odds of mortality were higher for people living in older building, likely to be less insulated, consistently through warm and cold temperatures. Women and people from older age groups were also at higher risk of heat-related cardiovascular mortality. Interestingly, we found gender-differential effect modification by education, especially relevant for women. These results are in line with previous studies reporting gender-differential effects of education level [Marí-Dell'Olmo et al. 2019] and age [Ragettli et al. 2017] on heat-related mortality. Previous research also reported higher heat-related mortality for women and for those with low education level in some age groups during the 2003 heatwave in Barcelona [Borrell et al. 2006], but no effect modification by indicators of socio-economic position in London [Murage et al. 2020]. While women lived longer than men in our study population (mean age at death = 84 vs. 74 years old), the age difference at death is unlikely to explain the full gender differential on mortality; stratified analyses also showed effect modification by age within women (Supplementary Table A.1). The observed increase in heat-related cardiovascular mortality for women with older age may also be related to post-menopausal status [Dratva et al. 2007], although the number of younger women (1.5% of all women were under 55 years old) was too limited in our study population to confirm this hypothesis. While the increased risk of heat-related mortality for men with higher socio-economic position cannot be fully explained, it may be related to differences in behaviour and lifestyle. Specifically behaviour such as drinking or reduced physical activity may explain some of the effect modification observed in our study (e.g. gender, marital status). Lower education may also be associated with more heat exposure at

work, lower health literacy, potentially higher prevalence of pre-existing conditions and lower adherence to behavioural adaptations during heat events.

A particular strength of this study is the combination of precise spatial and temporal individual exposures. While the case-crossover design is being increasingly used to investigate temperature and air pollution related health effects, many studies still use centrally monitored temperature data, similar to a time-series analysis [Buteau et al. 2018; Guo et al. 2011], or exposure data at coarser spatial resolution [Fu et al. 2018]. We used individual daily temperature and precipitation data at 2km resolution, and daily air pollution exposure data at 100 m resolution, which reduces the risk of exposure misclassification. A further strength of the study is the adjustment for aircraft noise, which minimizes potential bias as temperature and air pollution may each be correlated with aircraft noise. Case and control events are selected within the same month and following a time-stratified sampling scheme, limiting the risk of potential seasonal bias and adjusting by design. Specifically, individual characteristics which are stable over the short study time, such as age, socio-economic position, and long-term exposure to environmental pollutants are controlled. Combined with distributed lag linear models, this approach thus enables the investigation of the acute effects of temperature with minimum bias. Our findings generally agree with the existing literature, and offer additional understanding of the vulnerable groups for temperature-related mortality, including exposure to cold temperatures which have not yet been extensively studied in Switzerland. A potential limitation, however, is that our study population has been selected in Zurich, with higher proportions of those with high socio-economic position compared to the whole country. To confirm our results and extrapolate the findings to the general population, a larger proportion of individuals living in rural areas and other cultural and language regions should be conducted. As the strength of the association for cold-related mortality was weaker than for heat-related mortality, stratification and corresponding loss of power made it more difficult to identify potential effect modifiers for cold. Finally, we did not have the data to additionally investigate the interaction between heat and ozone levels in our study.

Conclusion

Our study shows that heat related mortality is more pronounced than cold related morality, and that temperature-related mortality varies depending on individual differ-

ences likely to be related to housing, social, physiological, and behavioural characteristics. Differences in environmental co-exposures also play a role in modifying the effects. Women of older age and with lower education and socio-economic position were found to be at highest risk for heat related cardiovascular mortality. Identification of the most vulnerable population groups under different exposure circumstances is essential to refine prevention campaigns in order to efficiently reduce temperature-related mortality. Climate shifts toward warmer temperatures may further increase the burden of heat-related mortality in many countries. Thus, effective public health measures are crucial to ensure heat-related mortality does not become an even larger problem in the future.

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Chapter 7

Mutual effects of particulate matter and nitrogen oxide on cause-specific acute cardiovascular mortality: a case-crossover study in Switzerland

Apolline Saucy[1,2], Kees de Hoogh[1,2], Danielle Vienneau[1,2], Louise Tangermann[1,2], Beat Schäffer[3], Jean-Marc Wunderli[3], Nicole Probst-Hensch[1,2], Martin Röösli[1,2]

[1] Swiss Tropical and Public Health Institute (Swiss TPH), Basel, Switzerland

[2] University of Basel, Basel, Switzerland

[3] Swiss Federal Laboratories for Materials Science and Technology (Empa), Dübendorf, Switzerland

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Mutual effects of fine particulate matter, nitrogen dioxide, and fireworks on cause-specific acute cardiovascular mortality: A case-crossover study in communities affected by aircraft noise☆

Apolline Saucy [a,b], Kees de Hoogh [a,b], Danielle Vienneau [a,b], Louise Tangermann [a,b], Beat Schäffer [c], Jean-Marc Wunderli [c], Nicole Probst-Hensch [a,b], Martin Röösli [a,b,*]

[a] Swiss Tropical and Public Health Institute (SwissTPH), Basel, Switzerland
[b] University of Basel, Basel, Switzerland
[c] Empa, Swiss Federal Laboratories for Materials Science and Technology, Dübendorf, Switzerland

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ABSTRACT

Ambient air pollution is the leading cause of environmental mortality and morbidity worldwide. However, the individual contributions to acute mortality of traffic-related air pollutants such as nitrogen dioxide (NO_2) and fine particulate matter ($PM_{2.5}$) are still debated. We conducted a time-stratified case-crossover study for a population located around Zurich airport in Switzerland, including 24,886 adult cardiovascular deaths from the Swiss National Cohort. We estimated the risk of cause-specific cardiovascular mortality associated with daily NO_2 and $PM_{2.5}$ concentrations at home using distributed lag models up to 7 days preceding death, adjusted for daily temperature, precipitation, acute night-time aircraft noise, firework celebrations, and holidays. Cardiovascular mortality was associated with NO_2, whereas the association with $PM_{2.5}$ disappeared upon adjustment for NO_2. The strongest association was observed between NO_2 and ischemic stroke mortality (odds ratio = 1.55 per 10 μg/m^3, 95% confidence intervals = 1.20–2.00). Cause-specific mortality analyses showed differences in terms of delayed effect: odds ratios were highest at 1–3 days after exposure for most outcomes but at lags of 3–5 days for heart failure. Individual vulnerabilities to NO_2 associated cardiovascular mortality also varied by cause of death, possibly highlighting the role of different behaviours and risk factors in the most susceptible groups. The risk of cardiovascular mortality was also increased on firework days and after public holidays, independent from NO_2 and $PM_{2.5}$ concentrations. This study confirms the association between ambient NO_2, as a marker for primary emissions, and acute cardiovascular mortality in a specific setting around a major airport. Future research should clarify the role of additional air pollutants including ultra-fine particles on cardiovascular diseases to inform most efficient control measures.

The authors declare they have no actual or potential competing financial interests.

1. Introduction

Ambient air pollution is one of the leading causes of mortality and morbidity worldwide (World Health Organization, 2018). According to the Global Burden of Disease, approximately 4.5 million deaths were directly attributable to air pollution in 2015 (Cohen et al., 2017). Air pollution is typically assessed based on a range of individual pollutants, including particulate matter of various size fractions (e.g. diameter less than 10 μm [PM_{10}] and less than 2.5 μm [$PM_{2.5}$]), nitrogen dioxide (NO_2), ozone (O_3), carbon monoxide (CO) and others. Of these pollutants, the largest part of the estimated excess mortality was attributed to particulate matter and ozone (World Health Organization, 2018; Brook et al., 2010). Chronic exposure to air pollution can affect cardiorespiratory health and cause heart and vascular damage, even at low levels

☆ This paper has been recommended for acceptance by Payam Dadvand.
* Corresponding author. Socinstrasse 57, 4051, Basel, Switzerland.
E-mail address: martin.roosli@swisstph.ch (M. Röösli).

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Abstract

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Introduction

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mortality was attributed to particulate matter and ozone [World Health Organization 2018a; Brook et al. 2010]. Chronic exposure to air pollution can affect cardiorespiratory health and cause heart and vascular damage, even at low levels [EPA., U.S. 2019; Schwartz, Bind, and Koutrakis 2017; Bourdrel et al. 2017]. Over time, such physiological damage and resulting chronic health conditions can set a susceptible ground for the development of cardiovascular health outcomes, which may be triggered by acute environmental conditions.

Besides chronic health effects, short-term exposure to ambient air pollution is associated with increased cardiovascular and respiratory mortality [Achilleos et al. 2017; Mustafic et al. 2012; Yang et al. 2015] and emergency visits and hospital admissions [Shah et al. 2013; Nawrot et al. 2011]. The causal association between particulate matter and acute mortality has been established, even at levels below the regulatory limits [EPA., U.S. 2019; Schwartz, Bind, and Koutrakis 2017]. However, establishing causality for specific air pollutants, which are often correlated, is a challenge. So far, the importance of acute $PM_{2.5}$ exposure over other common air pollutants in relation to all-cause mortality and respiratory health outcomes has been assessed using various analytical approaches. These include the use of instrumental variables [Schwartz, Bind, and Koutrakis 2017; Schwartz et al. 2015], the assessment of the stability of the initial effect estimates after adjusting for other pollutants, and the consistency of these results between seasons with varying correlation between the different pollutants [Sarnat et al. 2001]. While such studies established the short-term and independent contribution of $PM_{2.5}$ over NO_2 for respiratory diseases [Yang et al. 2015; Orellano et al. 2020], the independent contribution of NO_2 is still widely debated with regard to acute cardiovascular health outcomes [Mustafic et al. 2012; Chiusolo et al. 2011].

Some studies point towards a possible association of short-term NO_2 exposure with cardiovascular health outcomes, including acute myocardial infarction, cerebrovascular diseases, heart failure and mortality. For example, Mustafic et al. conducted a systematic review, including studies worldwide published until 2011, on the contribution of air pollution on acute myocardial infarction and reported a risk increase of 11% (95% confidence intervals (CI) = 6–16) per 10 $\mu g/m^3$ increase in short-term exposure to NO_2 [Mustafic et al. 2012]. However, as a result of insufficient studies focusing on the acute cardiovascular effects of NO_2, the US Environmental Protection Agency considered the evidence for premature mortality to be suggestive but insufficient to draw any causal pathway [EPA., U.S. 2016]. Similarly, in their systematic review, [Orellano et al. 2020]

reported associations between $PM_{2.5}$ and acute all-cause, cardiovascular, respiratory, and cerebrovascular mortality, but due to a lack of epidemiological studies on cardiovascular disease, NO_2 was only reported to be associated with all-cause mortality. More recently, studies have specifically investigated the joint effects of fine particulate matter and NO_2 on various health outcomes, including cardiovascular mortality, using multi-pollutant modelling approaches. While some report an independent effect of NO_2 on cardiovascular diseases [Costa et al. 2017; Chen et al. 2018; Linares et al. 2018; Tong et al. 2018], others support the overall importance of $PM_{2.5}$ and further gaseous pollutants over NO_2 [Qu et al. 2018; Liu et al. 2019]. In a study conducted in Northern China, [Liu et al. 2019] reported that NO_2 was more affected than $PM_{2.5}$ by mutual confounding in co-pollutant models. They also found a synergistic association between NO_2 and O_3, which may explain the absence of an independent effect observed for NO_2 in fully adjusted models.

It is thus still debated whether the association of short-term NO_2 exposure with acute cardiovascular health outcomes is independent of particulate matter exposure [Brook et al. 2007; Burnett et al. 2000]. To date, few studies analysed the mutual confounding between $PM_{2.5}$ and NO_2 in Europe, despite the fact that particulate matter may differ in its composition across regions, time and seasons [Mills et al. 2016]. For example, a stronger reduction in particulate matter than NO_2 was observed in recent years in Europe. Thus, NO_2 may have become an even stronger proxy for road traffic emissions including ultrafine particles (UFP) [Linares et al. 2018]. In addition, the composition of air pollution mixtures including UFP around airports and their individual contribution on cardiovascular health remains unclear. Precise individual exposure estimates are therefore required to investigate mutual pollution confounding and reduce the potential bias from using central monitoring for exposure assessment as typically used in previous studies on acute health effects [Sarnat et al. 2001]. Finally, epidemiological studies focusing on cause-specific cardiovascular mortality could help clarify the role of ambient air pollution on different cardiovascular diseases and their individual biological pathways.

The aim of this paper is to investigate the individual roles of NO_2 and $PM_{2.5}$ on cause-specific acute cardiovascular mortality in a population living in proximity to Zurich airport. We describe the mutual confounding between these two air pollutants, as well as with further environmental triggers of cardiovascular deaths, namely, temperature, precipitation, night-time aircraft noise, and planned fireworks.

Methods

Study population and design

We used data from the Swiss National Cohort (SNC), a longitudinal cohort based on linkage of national census data and complete mortality records for the Swiss population. The cohort contains mortality data (i.e. cause, date and time of death) as well as personal and housing information including age, sex, education, address history, building period and neighbourhood socio-economic position. We selected 24,886 adult cases of cardiovascular death (age >30) occurring between 2000 and 2015 with available address at time of death around Zurich airport, Switzerland. Zurich airport is a medium-sized airport with night curfew (ca. 270,000 flight movements each year between 2010 and 2016 [Zurich Airport 2021]). The study extent was selected using the envelope of the calculation perimeters for the Zurich Aircraft Noise Index of the years 2000–2015 [Saucy et al. 2020b] for the highly annoyed and the highly sleep disturbed persons [Schäffer et al. 2012], which covers an area with distances of up to 50 km around the airport (Supplementary Figure 1). We considered the following primary causes of death: all cardiovascular diseases (CVD) (ICD-10: I00-I99), ischaemic heart diseases (ICD-10: I20-I25), myocardial infarction (ICD-10: I21-I22), stroke (ICD-10: I60-I64), heart failure (ICD-10: I50), hypertensive diseases (ICD-10: I10-I15), and arrhythmias (ICD-10: I44-I49).

We used a case-crossover study design to investigate the individual and combined short-term effects of NO_2 and $PM_{2.5}$ on cardiovascular mortality in Switzerland. Each case of death was matched with three to four control days selected on the same day of the week within the same month, following a time-stratified control sampling [Janes, Sheppard, and Lumley 2005]. While time-series usually assigns exposure data from a central monitoring station, the case-crossover design enables the use of precise individual daily air pollution estimates at home location, taking advantage of the precise spatiotemporal estimates calculated in this study.

Exposure data

As ambient air pollution data source, we used previously modelled daily NO_2 and $PM_{2.5}$ at 100 × 100 m resolution in Switzerland, available for the years 2005-2015 and 2003-2013 respectively [De Hoogh et al. 2019; De Hoogh et al. 2018]. The exposure esti-

Table 7.1: Summary statistics of the characteristics of all deaths included in the study with respect to the NO_2 and $PM_{2.5}$ distribution on the day of death and control days.

	N (%)	NO_2 [µg/m³]			$PM_{2.5}$ [µg/m³]		
Percentiles		**25th**	**50th**	**75th**	**25th**	**50th**	**75th**
Cause of death							
All-cause cardiovascular	24886 (100)	14.09	22.55	33.03	11.14	16.24	23.63
Ischaemic heart diseases	10521 (41)	14.27	22.58	32.98	11.35	16.52	23.97
Myocardial infarction	3248 (13)	13.71	22.29	33.05	11.21	16.28	24.18
Stroke	3750 (15)	14.29	23.15	34.11	11.28	16.61	24.08
Heart failure	1753 (7)	13.69	21.99	32.74	11.04	15.93	23.97
Hypertensive diseases	2728 (11)	14.20	22.70	33.11	10.74	15.58	22.83
Arrhythmias	1392 (6)	13.35	22.02	32.85	11.14	15.99	22.70
Gender							
Female	13269 (53)	14.22	22.89	33.37	11.17	16.33	23.68
Male	11617 (47)	13.89	22.20	32.64	11.11	16.13	23.55
Age groups							
<=75	5632 (23)	13.72	22.29	32.83	11.32	16.36	24.02
75-85	8324 (33)	14.37	22.68	32.98	11.13	16.29	24.02
>85	10930 (44)	14.01	22.57	33.22	11.08	16.16	23.12
*Socio-economic position**							
1	2512 (10)	18.19	27.51	38.35	12.16	17.15	24.90
2	3685 (15)	15.24	24.20	34.59	11.89	17.11	24.75
3	4470 (18)	14.44	22.50	33.46	11.19	16.47	23.89
4	6263 (25)	13.76	22.03	32.11	11.03	16.11	23.45
5	6572 (26)	12.24	20.40	30.26	10.33	15.22	22.11
Unknown	1384 (6)	13.93	22.36	33.11	12.20	17.47	25.03
Education							
Compulsory or less	8830 (35)	14.22	22.64	33.22	11.39	16.62	23.87
Upper secondary level	12353 (50)	14.27	22.85	33.36	11.14	16.22	23.68
Tertiary level	3150 (13)	13.07	21.20	31.14	10.56	15.34	22.77
Unknown	553 (2)	13.83	22.84	33.39	10.50	15.43	23.14
Urbanisation							
Urban	9108 (36)	19.56	29.05	38.97	12.13	17.38	25.13
Peri-urban	14347 (58)	12.46	20.00	29.18	10.79	15.77	22.89
Rural	1431 (6)	8.56	14.42	21.57	9.35	13.87	20.68
Building period							
Before 1970	14957 (60)	14.71	23.45	33.85	11.50	16.79	24.29
1970-1990	7082 (28)	13.38	21.67	31.77	11.03	15.95	23.00
After 1990	2372 (10)	13.00	21.17	31.12	10.07	14.96	22.04
Unknown	475 (2)	10.56	18.29	28.39	9.01	13.29	20.25
Civil status							
Married	9286 (37)	13.71	21.75	32.32	11.20	16.21	23.52
Non-married	15600 (63)	14.29	23.09	33.45	11.12	16.27	23.68

* Neighbourhood socio-economic position (SEP) index ranging from lowest (0) to highest (100), displayed as quantiles (Q1 to Q5) [Panczak et al. 2012].

mates are based on a four-stage modelling strategy, combining daily monitored NO_2 and $PM_{2.5}$ data across Switzerland from the regulatory monitoring network for Switzerland,

NABEL [*NABEL National Air Pollution Monitoring Network* 2001], satellite-based data from the Ozone Monitoring Instrument (OMI) [OMINOA Team 2016] for NO_2, , Multi-Angle Implementation of Atmospheric Correction (MAIAC) spectral AOD data derived from MODIS at 1×1 km resolution for $PM_{2.5}$ [Lyapustin et al. 2011], and further spatial and temporal predictor data including traffic intensity, road density, land use, altitude, Normalized Difference Vegetation Index (NDVI), annual emissions, and daily meteorological data. An adapted modelling strategy was used to extend the exposure model of $PM_{2.5}$ at 100×100 m resolution to the years 2014-2016after the original time-series, needed for this study (Supplementary materials).

We used daily NO_2 and $PM_{2.5}$ at home location for all case and control events. To include individual daily exposure estimates for the earliest years in the time series not covered by the original models (2000–2002 for $PM_{2.5}$ and 2000–2004 for NO_2), we applied the following two-stage modelling approach: first, we calibrated the spatial distribution of the annual average concentrations at home location for the first available modelled year with the daily values from routinely collected data at Dübendorf monitoring station (7.1). In a second step, the estimates calculated in (7.1) were refined using a random forest modelling approach calibrated with daily values from Dübendorf monitoring station, Julian day, and x and y coordinates (7.1).

$$P_{i,j} = P_{j,mean} - P_{D,mean} + P_{D,i} \tag{7.1}$$

- Where $P_{i,j}$ is the air pollution estimate calculated on day i and location j;
- $P_{j,mean}$ is the yearly average estimate at location j for the first available year of the 100×100 m resolution model;
- $P_{D,mean}$ is the yearly average estimate from Dübendorf monitoring station for this same year;
- $P_{D,i}$ is the daily estimate monitored at Dübendorf station on day i.

$$P_{RF} = P_{i,j} + P_{D,i} + x_j + y_j + jd_i \tag{7.2}$$

- Where P_{RF} is the final pollution estimate calculated by random forest;
- $P_{i,j}$ is the exposure estimate on day i and location j as calculated in (7.1);
- $P_{D,i}$ is the daily estimate monitored at Dübendorf station on day i;
- x_j and y_j are the x and y coordinates from location j;

- jd_i is the Julian day on day i.

We used 2 × 2 km meteorology data from MeteoSwiss (Grid-Data Products) and assigned daily outdoor mean temperature (Tmean) and precipitation at home location [MeteoSwiss 2017; MeteoSwiss 2016]. Night-time aircraft noise exposure was calculated at home locations for the case and control nights by combining a list of all aircraft movements at Zurich airport between 2000 and 2015 with precise outdoor aircraft noise exposure calculations at 250 × 250 m or specific aircraft types and air routes, as previously described in [Saucy et al. 2020b]. Building on our analysis of the acute noise effects on mortality [Saucy et al. 2020a], we used the average aircraft noise exposure (L_{Aeq}) during the night preceding daytime deaths and the average noise exposure within 2h preceding night-time deaths. To make these comparable prior to confounding adjustment, we normalized the acute noise exposure values before aggregating the corresponding z-values into a single exposure measure.

Statistical analyses

We investigated the acute and delayed (up to seven days) effects up to seven days of daily NO_2 and $PM_{2.5}$ concentrations on cardiovascular mortality using a distributed lag modelling approach (DLM). We modelled lag-specific association between ambient air pollution and cause-specific cardiovascular mortality using the 'dlnm' package [Gasparrini 2011]. We specified the lag function as a natural spline with two equally spaced knots on the logarithmic scale. We estimated the lag-specific and cumulative (over 7-days lag) odds of mortality per 10 $\mu g/m^3$ increase in NO_2 and $PM_{2.5}$ separately. Both DLM models were adjusted for the other pollutant, as well as for 3-days average temperature ($T_{mean}+(T_{mean})^2$), daily precipitation, night-time normalized aircraft noise, national holidays (lags 0 and 1) and national firework days (August 1st and December 31st, lags 0 and 1). We investigated mutual confounding and confounding by other short-term environmental exposures (night-time aircraft noise and temperature) by removing each covariate in turn, thus reporting the cumulative odds ratio (OR) for NO_2 and $PM_{2.5}$, identified as meaningful from the DLM and validated using Akaike's criterion (AIC). This simplified multiple exposures model enabled us to investigate effect modification between air pollution and cardiovascular mortality by individual characteristics (e.g. age, sex, socio-economic position, education, marital status) by introducing, in turn, each individual interaction term (Supplementary Equation S.1). To support the findings from individual interaction analyses, sensitivity analysis was performed by creating additional

models combining several interaction terms including age, education, and socio-economic position. All analyses were performed using conditional logistic regression in R version 4.0.2, 'survival' package.

Results

We identified 24,886 cases of adult (age >30 years) deaths from cardiovascular cause from the SNC between 2000 and 2015. Median daily NO_2 and $PM_{2.5}$ were 23 and 16 $\mu g/m^3$ respectively. Both NO_2 and $PM_{2.5}$ levels were higher in the lower socio-economic groups and in urban and peri-urban settings (Kruskal-Wallis test, $p < 0.01$). The two pollutants did not differ between the other population subgroups presented in Table 7.1. Pearson correlation coefficient between daily NO_2 and $PM_{2.5}$ levels was 60% (Supplementary Figure 2 shows a detailed correlation matrix for all lags and exposure variables).

Table 7.2: OR of cardiovascular mortality for all and cause-specific cardiovascular deaths per 10 $\mu g/m^3$ increase in NO_2, cumulative over 0–7 lag days. Statistically significant results (α=5%) are marked in bold.

Cause of death	**NO_2 Model 1** [1)]	**NO_2 Model 2** [2)]	**NO_2 Model 3** [3)]	**NO_2 Model 4** [4)]
All cardiovascular diseases	**1.05 (1.01-1.10)**	**1.03 (1.00-1.07)**	**1.05 (1.01-1.10)**	**1.04 (1.00-1.09)**
Ischaemic heart diseases	1.05 (0.99-1.13)	1.03 (0.98-1.08)	1.05 (0.99-1.13)	1.04 (0.97-1.11)
Myocardial infarction	1.08 (0.95-1.22)	1.02 (0.93-1.12)	1.08 (0.95-1.22)	1.06 (0.94-1.20)
Stroke	**1.13 (1.01-1.26)**	**1.14 (1.05-1.23)**	**1.13 (1.01-1.26)**	**1.13 (1.02-1.26)**
Haemorrhagic stroke	1.03 (0.81-1.31)	1.11 (0.93-1.32)	1.03 (0.81-1.31)	1.06 (0.84-1.34)
Ischaemic stroke	**1.55 (1.20-2.00)**	**1.41 (1.17-1.71)**	**1.55 (1.2-02.00)**	**1.46 (1.14-1.87)**
Hypertensive	0.97 (0.82-1.13)	0.97 (0.86-1.10)	0.96 (0.82-1.13)	0.97 (0.83-1.14)
Heart failure	1.09 (0.95-1.24)	1.04 (0.94-1.15)	1.09 (0.95-1.24)	1.07 (0.94-1.22)
Arrhythmias	0.90 (0.75-1.09)	0.95 (0.82-1.09)	0.90 (0.74-1.08)	0.90 (0.75-1.08)

1) Model 1 (Main Model) is adjusted for $PM_{2.5}$, temperature, precipitation, night-time aircraft noise, holidays and firework days.

2) Model 2: Main Model without adjustment for $PM_{2.5}$.

3) Model 3: Main Model without adjustment for aircraft noise.

4) Model 4: Main Model without adjustment for temperature.

The associations between ambient air pollutants and cause-specific cardiovascular mortality from the distributed lag models are presented in Table 7.2 and Table 7.3. In the mutually adjusted models (main models), only NO_2 was significantly associated with an increase in the odds of cardiovascular mortality, showing a 5% increase in the odds of mortality for each increase in 10 $\mu g/m^3$ (OR NO_2 = 1.05 [1.01–1.10]; OR $PM_{2.5}$ =

Table 7.3: OR of cardiovascular mortality for all and cause-specific cardiovascular deaths per 10 $\mu g/m^3$ increase in $PM_{2.5}$, cumulative over 0–7 lag days. Statistically significant results (α=5%) are marked in bold.

Cause of death	$PM_{2.5}$ Model 1 [1)]	$PM_{2.5}$ Model 2 [2)]	$PM_{2.5}$ Model 3 [3)]	$PM_{2.5}$ Model 4 [4)]
All cardiovascular diseases	0.99 (0.95-1.02)	1.01 (0.99-1.04)	0.99 (0.95-1.02)	1.00 (0.97-1.03)
Ischaemic heart diseases	0.98 (0.92-1.03)	1.01 (0.97-1.06)	0.98 (0.92-1.03)	1.00 (0.95-1.05)
Myocardial infarction	0.96 (0.87-1.07)	1.01 (0.93-1.09)	0.96 (0.87-1.07)	0.98 (0.89-1.08)
Stroke	1.01 (0.92-1.11)	**1.08 (1.01-1.15)**	1.01 (0.92-1.11)	1.01 (0.93-1.09)
Haemorrhagic stroke	0.94 (0.78-1.14)	1.01 (0.88-1.17)	0.94 (0.78-1.14)	0.89 (0.75-1.07)
Ischaemic stroke	1.02 (0.81-1.27)	**1.21 (1.03-1.43)**	1.02 (0.81-1.27)	1.12 (0.91-1.37)
Hypertensive	1.02 (0.89-1.16)	0.98 (0.89-1.08)	1.02 (0.89-1.16)	1.01 (0.89-1.14)
Heart failure	0.94 (0.84-1.05)	0.97 (0.90-1.06)	0.95 (0.85-1.06)	0.97 (0.88-1.08)
Arrhythmias	1.02 (0.87-1.20)	0.95 (0.84-1.07)	1.02 (0.87-1.20)	1.03 (0.89-1.19)

1) Model 1 (Main Model) is adjusted for NO_2, temperature, precipitation, night-time aircraft noise, holidays and firework days.

2) Model 2: Main Model without adjustment for NO_2.

3) Model 3: Main Model without adjustment for aircraft noise.

4) Model 4: Main Model without adjustment for temperature.

0.90 [0.95–1.02]). The risk estimates from the NO_2 single-pollutant models remained stable with and without adjustment for $PM_{2.5}$ (Main Model vs. Model 2 in Table 7.2). The strongest association with NO_2 was observed for ischaemic stroke (OR NO_2 = 1.55 [1.20–2.00]). Suggestive associations were also observed for ischaemic heart diseases, myocardial infarction, heart failure and haemorrhagic stroke in relation to NO_2 concentrations; no association for deaths due to hypertensive diseases and arrhythmia were found. For most diagnoses, the strongest association with NO_2 was observed for lag days 1–3. The shape of the lag-mortality response was distinct for heart failure, with reduced OR for lag day 1 and increased OR for lag days 3–5 (Figure 7.1). In contrast, the effect estimates for $PM_{2.5}$ moved towards OR = 1 when adjusting for NO_2, and none of the cause specific associations with $PM_{2.5}$ were significant in the multi-pollutant models (Main Model in Table 7.3).

The OR coefficients of all exposures included in the multi-pollutant models remained stable through adjustment by the covariates aircraft noise and temperature (Models S2 and S3 in Table 7.2 and Table 7.3). Similar, the risk estimates remained stable with and without adjustment for precipitation, firework days and national holidays. Overall, except two significant risk estimates for $PM_{2.5}$ disappearing after co-adjustment by NO_2 (Model 2 in Table 7.2), there was only limited mutual confounding between the different short-term exposures (acute night-time aircraft noise, NO_2, $PM_{2.5}$, firework days and

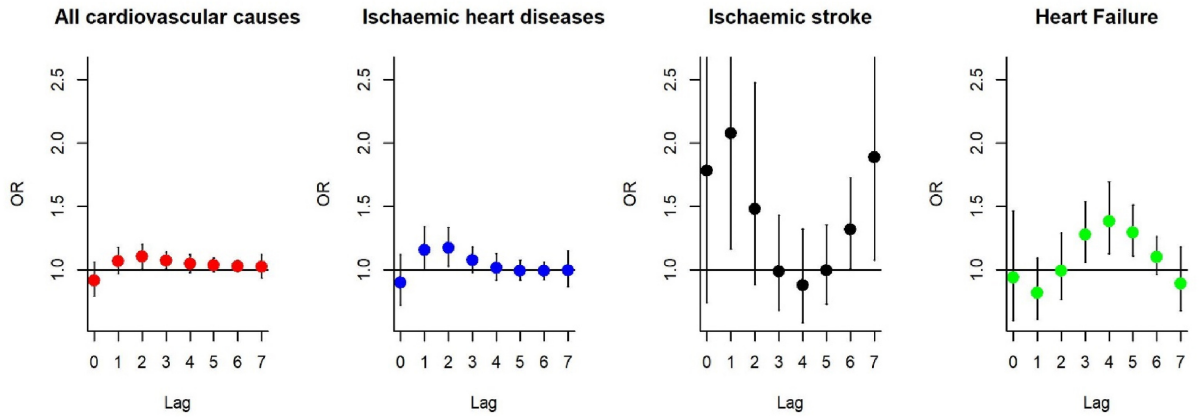

Figure 7.1: Odds ratios (ORs) of mortality associated with daily NO_2 (lag days 0 to 7) for all-cause cardiovascular mortality and for specific diagnoses (ischaemic heart diseases, stroke, and heart failure). Models adjusted for $PM_{2.5}$, temperature, precipitation, night-time aircraft noise, holidays, and firework days.

national holidays) in association with acute cardiovascular mortality (Supplementary Table S1).

Based on the results from the distributed lag models (Table 7.2 and Table 7.3), we created a multi-pollutant model using air pollution levels (NO_2 and $PM_{2.5}$) averaged over lags 0 to 4 for all cardiovascular deaths (Table 7.4, Overall Model). Correlation between daily NO_2 and $PM_{2.5}$ was 60%, but the variation inflation factor (VIF) remained below 3 for all variables. From this model, the OR for cardiovascular mortality was 1.04 (95% CI = 1.00–1.08) for NO_2 and 0.98 (95% CI = 0.95–1.02) for $PM_{2.5}$, which closely corresponds to the values of the Main Models in Table 7.2 and Table 7.3. Since only NO_2 was associated with an increased risk of mortality in the fully adjusted model, interaction analysis was performed for this pollutant only. An increased OR was also observed for all cardiovascular deaths in relation to national firework days (August 1st and December 31st) (OR = 1.29 [1.08–1.54]) and national public holidays with lagged effect for the day after (OR^{lag0} = 0.98 [0.89–1.08]; OR^{lag1} = 1.08 [0.99–1.18]).

We did not observe any effect modification for the association between 4-day average NO_2 and all cardiovascular deaths by sex, education, or socio-economic position. The OR of cardiovascular mortality was increased for younger age and for the civil status married (Table 7.4). Though the interaction terms did not significantly indicate effect modification, the OR of ischaemic stroke mortality was increased for males, lower neigh-

Table 7.4: OR of mortality associated per 10 µg/m^3 increase in 4-day average NO_2 concentrations at home location for different groups of the population and causes of death. Models adjusted for $PM_{2.5}$, temperature, precipitation, night-time aircraft noise, holidays and firework days. Statistically significant results (α = 5%) are marked in bold. Interaction terms for continuous variables (e.g. age, socio-economic position) were introduced as linear interaction variables, and ORs are reported for different levels within the range of the interaction variable.

Groups	All CVD (N=24,886)	p-int	Myocardial infarction (N=3,248)	p-int	Heart failure (N=2,728)	p-int	Ischaemic stroke (N=627)	p-int
Overall	1.04 (1.00-1.08)		1.08 (0.97-1.20)		1.05 (0.94-1.19)		**1.35 (1.07-1.69)**	
Sex		0.64		0.95		0.33		0.33
Males	**1.05 (1.00-1.10)**		1.08 (0.95-1.22)		1.00 (0.85-1.17)		**1.48 (1.10-1.99)**	
Females	1.04 (0.99-1.09)		1.09 (0.94-1.25)		1.09 (0.95-1.24)		1.28 (0.99-1.64)	
Age		**0.04**		0.64		**0.04**		**0.03**
60	**1.10 (1.04-1.17)**		1.04 (0.88-1.19)		**1.28 (1.06-1.50)**		**1.96 (1.55-2.36)**	
75	**1.06 (1.02-1.10)**		1.07 (0.96-1.19)		**1.14 (1.00-1.27)**		**1.52 (1.26-1.77)**	
90	1.02 (0.98-1.07)		1.12 (0.98-1.25)		1.00 (0.88-1.13)		1.17 (0.91-1.43)	
*Building period**								
Before 1970	**1.05 (1.00-1.09)**	0.34	1.09 (0.97-1.24)	0.93	1.06 (0.92-1.21)	0.45	1.23 (0.96-1.58)	0.16
1970-1990	1.04 (0.98-1.10)		1.08 (0.92-1.27)		1.07 (0.90-1.27)		**1.84 (1.29-2.63)**	
After 1990	1.07 (0.98-1.10)		1.00 (0.76-1.32)		1.11 (0.83-1.48)		1.16 (0.62-2.17)	
*Socio-economic position***		0.93		0.25		0.54		0.27
10	1.05 (0.89-1.21)		1.40 (0.93-1.86)		1.23 (0.73-1.73)		**2.26 (1.33-3.20)**	
50	1.04 (0.98-1.11)		1.16 (0.99-1.34)		1.10 (0.92-1.29)		**1.58 (1.22-1.94)**	
90	1.04 (0.96-1.11)		0.97 (0.76-1.18)		0.99 (0.76-1.23)		1.10 (0.67-1.54)	
Education								
Compulsory or less	1.02 (0.97-1.08)	0.74	1.01 (0.86-1.18)	0.60	1.00 (0.85-1.16)	0.59	1.08 (0.79-1.48)	0.18
Upper secondary	**1.05 (1.00-1.10)**		**1.13 (1.00-1.29)**		1.08 (0.93-1.24)		**1.46 (1.12-1.90)**	
Tertiary	1.06 (0.98-1.15)		1.05 (0.85-1.29)		1.20 (0.91-1.57)		**1.72 (1.08-2.75)**	
Civil status		**0.05**		0.53		0.64		0.38
Married	**1.08 (1.03-1.14)**		1.11 (0.97-1.27)		1.02 (0.86-1.22)		**1.45 (1.09-1.94)**	
Non-married	1.02 (0.98-1.07)		1.06 (0.93-1.20)		1.07 (0.94-1.21)		1.27 (0.98-1.65)	

* P-value from the interaction term with NO_2 (p-int).
** Neighbourhood socio-economic position (SEP) index ranging from lowest (0) to highest (100) [Panczak et al. 2012].

bourhood socio-economic position, and higher education groups. In contrast, the OR of mortality from myocardial infarction was highest for older age.

Based on the results from the distributed non-linear lag models, we could create a multi-pollutant model using air pollution levels averaged over lags 0 to 4 for all cardiovascular deaths. Correlation between daily NO_2 and $PM_{2.5}$ was 60% but the variation inflation factor (VIF) remained below 3 for all variables. From this model, the OR for cardiovascular mortality was 1.04 (95% CI = 1.00-1.08) for NO_2 and 0.98 (95% CI = 0.95-1.02) for $PM_{2.5}$. Increased OR of all-cause cardiovascular mortality was observed in relation to national firework days (August 1st and December 31st) (OR_{lag0} =1.29, p<0.01; OR_{lag1} = 1.08, p=0.39) and after national public holidays (OR_{lag0} = 0.97 p=0.5; OR_{lag1}=1.08, p=0.08). The overall model was improved with the introduction of nor-

malized night-time aircraft noise (AIC fully adjusted model = 73429.90 versus 73430.15 without adjusting for aircraft noise).

We did not observe any effect modification for the association between 4-days average NO_2 and all-cause cardiovascular mortality by sex, education and socio-economic position. The OR of cardiovascular mortality was increased for younger age and for the civil status married (Table 7.4). In addition, the OR of ischaemic stroke mortality was also increased for males, lower socio-economic position, and higher education groups. In contrast, the OR of mortality from myocardial infarction was highest for older age, even though not statistically significant (p-interaction = 0.64).

Discussion

Summary and main findings

The aim of this study was to assess the mutual independent associations of short-term NO_2 and $PM_{2.5}$ with cause-specific cardiovascular mortality in Switzerland while adjusting for the acute effect of other environmental exposures with adverse cardiovascular health effects. In single pollutant models NO_2, and to a lesser extent $PM_{2.5}$, was associated with all cardiovascular deaths or specific causes of death for a cumulative exposure lag-period of 7 days preceding death. However, two-pollutant models point to an association with NO_2 but not $PM_{2.5}$. The largest point estimate was observed between NO_2 and ischemic stroke mortality.

Confounding in the multiple exposures models

The distributed lag model was useful to identify the most relevant exposure period for each health outcome and inform the multi-pollutant model. The two approaches were equivalent and yielded similar risk estimates (OR NO_2 = 1.04 [1.00–1.08] for the multi-pollutant model based on 4-day average air pollution levels and OR NO_2 = 1.05 [1.01–1.10] for the distributed lag model). Overall, most of the observed increase in cardiovascular mortality could be attributed to NO_2. On the other hand, the association between $PM_{2.5}$ and cardiovascular mortality was strongly reduced when adjusting for NO_2, leaving only little individual effect of $PM_{2.5}$ in this study. The models did not show much auto-correlation (VIF) between these two variables, supporting the relevance of NO_2 for acute cardiovascular mortality.

Air pollution mixtures and the composition of fine particulate matter are subject to large variations across regions and may depend on the major types of pollution sources. Few studies have systematically assessed the mutual confounding between NO_2 and $PM_{2.5}$ in Europe or in regions exposed to air traffic related pollution. Our study thus contributes to a better understanding of the short-term effects of combined particulate matter and NO_2 on cardiovascular mortality in populations living near a major airport, where an increased contribution of UFP can be expected [Rivas et al. 2020]. In this context, NO_2 may thus be a proxy measure of other, unmeasured vehicle emissions such as air-traffic related UFP or volatile organic compounds [Brook et al. 2007]. This may explain our somewhat different results with previous studies, mostly observing associations of $PM_{2.5}$ with acute cardiovascular mortality [Schwartz et al. 2015; Orellano et al. 2020; Liu et al. 2019; Lee, Kim, and Lee 2014]. Nevertheless, the causal role of NO_2 for acute cardiovascular mortality may be supported by its gaseous nature and quick passage into the bloodstream [EPA., U.S. 2016]. Generally, increased knowledge on the physiological action of NO_2, UFP, and particulate composition on the cardiovascular system is needed to interpret and disentangle the underlying origins of cause-specific cardiovascular mortality.

Compared to previous studies, air pollution concentrations in our study population were rather low, and exposure was specifically modelled for the place of residence using spatiotemporal models, yielding more precise individual estimates as opposed to the more simple approach to use central monitors [Chiusolo et al. 2011; Samoli et al. 2006]. With this spatial resolution, NO_2 may be an important primary air pollution indicator for traffic including UFP from the airport or for secondary pollutants like O_3, not included in this study. For instance, [Luo et al. 2016] reported greater health effects in association with NO_2 in highly populated areas and increased civil air traffic than in rural areas. [Peters et al. 2004] observed an association between time spent in traffic and acute myocardial infarction. UFP, a pollutant easily crossing the alveoli-capillary barrier, may therefore be more relevant than $PM_{2.5}$ with regards to acute cardiovascular mortality. In Switzerland, $PM_{2.5}$ is predominantly an indicator of background air pollution resulting to a large extent from long range air transport [Federal Office for the Environment 2020b]. With urban population and air traffic density expected to increase [Güneralp et al. 2017], it is especially important to further disentangle the individual contributions of NO_2, $PM_{2.5}$, and UFP as well as particle composition on cardiovascular health to inform future health policies.

To the best of our knowledge, this is the first study to adjust for acute aircraft noise in air pollution studies. For long-term exposure, [Héritier et al. 2018] provided evidence that the association between NO_2 and particulate matter in Switzerland was confounded by transportation noise. In this study, we did not find an indication of confounding of the association between short-term air pollution and cardiovascular mortality by short-term night-time aircraft noise. Further, no confounding is to be expected from long-term environmental exposures due to the individual matching in this case-crossover study. We found that for acute cardiovascular mortality, the different environmental exposures investigated here were rather stable, showing no sign of mutual confounding. This confirms that at least on the short term, the cardiovascular effects of NO_2, night-time aircraft noise, temperature and precipitation are independent from each other.

The risk of cardiovascular mortality was increased by 29% on 'firework' days (August 1st and December 31st), independent from NO_2 and $PM_{2.5}$ concentrations, which is in line with [Greven et al. 2019]. Fireworks on national day and New Year's eve are known to affect ambient air quality [Godri et al. 2010; Seidel and Birnbaum 2015], but this observed excess mortality may also be the consequence of specific behaviours (e.g. excess consumption of food and alcohol, lack of sleep) or firework associated noise exposure, which may be the reason for the different lag structure compared to air pollution.

Cause-specific cardiovascular mortality in relation to ambient air pollution

While ischaemic and haemorrhagic strokes are often considered as a single group of diseases in epidemiological studies, they may be caused by different underlying physiological mechanisms, resulting in differential association with air pollution [Bourdrel et al. 2017; Wichmann and Voyi 2012]. In this study, we observed a strong risk increase for ischaemic but not haemorrhagic stroke in association with ambient NO_2, supporting the differential action of environmental exposures on these two disease groups. Despite a relatively small sample size, the association between NO_2 and ischaemic stroke was strongly significant due to a large effect size, but reduced power may explain the inconclusive results observed for arrhythmias. More generally, the risk of mortality was increased for all disease groups involving some type of ischaemia (i.e. ischaemic heart diseases, myocardial infarctions and ischaemic strokes), coherent with the suspected physiological response described for NO_2, including acute inflammation, and increased coagulation. However, the cardiorespiratory physiological changes in response to NO_2 exposure need

to be further studied and described, as specific knowledge is currently limited [EPA., U.S. 2016].

Unlike a previous study, which reported an increased risk of heart failure associated with same-day NO_2 and $PM_{2.5}$ levels [Shah et al. 2013], we found that the risk of heart failure in association with NO_2 was highest 3–5 days after exposure, following an initial risk reduction. The physiology of heart failure is different from the ischaemic events. Patients with heart failure have already been described to be at higher risk of cardiovascular mortality in association with air pollution, mainly due to subsequent increased heart rate and diastolic blood pressure [Buteau et al. 2018; Goldberg et al. 2015; Goldberg et al. 2011]. In a previous study, we demonstrated that the association between heat and mortality from heart failure was modified by the presence of ambient air pollution [Saucy et al. 2021]. A generalized vasodilatation and volume depletion as a response to a heat event may explain the initial risk decrease in our study population, followed by increased mortality in relation to the combined stress event.

Air pollution levels were associated with the same acute cardiovascular diagnoses as previously observed for short-term night-time aircraft noise [Saucy et al. 2020a], highlighting some common pathophysiological mechanisms as a response to short-term air pollution and aircraft noise, both suspected to be involved in vascular oxidative stress reactions [Bourdrel et al. 2017; Münzel et al. 2020b]. However, aircraft noise exposure in the night preceding death events did not affect the risk of NO_2 associated cardiovascular mortality.

Effect modification and vulnerability groups

The distribution of $PM_{2.5}$ and NO_2 was uneven with respect to socio-economic position, with higher pollution levels in locations with lower socio-economic position, showing that social inequity related to air quality reported in previous studies [Fairburn et al. 2019] was also present in our study population. Individual vulnerabilities to NO_2 related mortality varied across the specific causes of death, highlighting potential variations of risk factors in relation to these different pathologies. For example, social determinants of health such as sex, education and socio-economic position did not modify the short-term association between NO_2 and all cardiovascular deaths. Despite a higher susceptibility to cardiovascular mortality with older age (mean age was 80 years old in our study population), the relative acute risks were lower in the oldest age groups. This observation was

consistent for heart failure and ischaemic stroke, but not for myocardial infarction, where the OR (non-significantly) increased with older age. In these three groups of diseases, increased susceptibility was observed for people with lower socio-economic position, who were also exposed to increased levels air pollution and were therefore more vulnerable to air pollution overall. In contrast, increased OR was only observed with increasing education for ischaemic stroke, possibly in relation with specific behaviours and risk factors in this group of the population. Sensitivity analysis including multiple interactions suggest that the described effect modification by education and socio-economic position is not influenced by differential age and sex in these groups.

Strenghts and limitations

While time-series analyses rely on centralized data from monitoring stations, the case-crossover design enables the use of individual exposure data, considering spatial fluctuations at different locations on a daily basis, which is an asset of this study. The NO_2 and $PM_{2.5}$ exposure data used in this study were extracted at home location from longitudinal nationwide air pollution models with high spatial and temporal resolution, thus minimizing potential exposure misclassification. Due to the individual matching between case and control events within a short period of one month, all analyses were adjusted by design for individual characteristics such as age, sex, and socio-economic position. Combined with distributed lag models, this approach enabled us to investigate the delayed cause-specific exposure-response between ambient air pollution and cardiovascular mortality with minimum bias. Potential confounders that also vary over a short time, such as meteorological conditions, were similarly included from high resolution models designed for Switzerland. This study additionally adjusts for acute environmental (specifically aircraft) noise, which is rarely considered in air pollution studies, but has been described as a potential confounder on the association between long-term air pollution exposure and cardiovascular mortality.

A limitation of this study is that we did not include ozone, ultra-fine particles and relative humidity, as they were not available in our study area at a similar spatial resolution. Our study population was selected around Zurich airport (up to 50 km distance), which is an interesting setting from an air pollution emission perspective with possible specific air pollution mixtures in relation to air traffic. While this choice may limit the generalization of our results to other neighbourhoods, not exposed to air traffic, it offers unique information for future discussion of health outcomes in various exposure

settings. Finally, a larger range of urbanization levels, language regions, and socio-economic positions would also be necessary for the generalization of our results to the broader Swiss population. Similar studies focusing on populations exposed to intense air traffic should help support our findings and the role of unmeasured traffic-related pollutants for cardiovascular mortality.

Conclusion

Based on precise individual exposure estimates and a robust study design, this study confirms the association between short-term ambient NO_2 and acute cardiovascular mortality in a specific setting around a major airport. The association between $PM_{2.5}$ and cardiovascular mortality was strongly reduced when adjusting for NO_2, leaving only little individual effect of $PM_{2.5}$. Future research should further investigate the role of different air pollutants such as UFP emitted by the air traffic as well as particles composition in relation to acute cardiovascular diseases to inform most efficient control measures.

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Part IV

Discussion

Chapter 8

General discussion

'One day, mankind will have to fight noise as relentlessly as Cholera and Pest'

Robert Koch (1843 – 1910)

The overall aim of this thesis was to understand the role of night-time aircraft noise events on acute cardiovascular mortality. Through this work, I was able to contribute to the growing body of evidence on the timing of response to acute noise events during the night by providing first-ever estimates of the association between night-time aircraft noise exposure and acute fatal coronary events. The research presented in this thesis sets the foundations to refine future aircraft noise regulations and to tailor public health responses to the specific characteristics of night-time aircraft noise.

It is a recurrent criticism that research on the health effects of noise is potentially biased by insufficient adjusting for individual characteristics. By associating a case-crossover design with an informative and sound dataset of individual noise exposure around Zurich Airport, I could overcome this criticism and address the main research question using a combination of strong methodological and statistical approaches. In addition, the exposure-response relationship analysis offers a deeper understanding of the role of low levels of night-time noise on different cardiovascular health outcomes. It also supports the effective translation of previously described physiological changes in response to aircraft noise to acute fatal cardiovascular events.

Taking advantage of other precise individual exposures calculated for this research such as meteorological conditions and air pollution, I was not only able to adjust for them, but also to investigate their individual and combined associations with acute cardiovascular mortality. Throughout this thesis, I attached particular importance to the identification and characterisation of specific vulnerability groups in relation to air-

craft noise, temperature, and air pollution exposures. Further, the developed multiple-exposure models and interaction analyses contribute to a broader understanding of close to real-life combined environmental exposures and their individual contributions as triggers of cardiovascular death (Figure 8.1).

By quantifying the contribution of night-time noise on cardiovascular mortality and identifying vulnerable groups of the population with regard to several environmental exposures, this thesis can help inform future public health policies and promote environmental health equity. The following sections provide a general discussion of the findings presented in this thesis, followed by a reflection of their overall public health relevance in light of current and future environmental challenges.

Figure 8.1: Overview of the living environment and multiple environmental exposures, as experienced by communities living in the vicinity of a major airport. Illustration: Fabienne Fischer.

8.1 Night-time aircraft noise as a trigger of cardiovascular death

Environmental noise has been increasingly gaining the public interest over the past couple of years (examples in Appendix E). The impact of airports on the local population, both in terms of air and noise pollution, as well as flight restrictions during the night hours, are still giving rise to a number of heated debates. With air traffic expected to increase in coming years, it is particularly important to gather a broad understanding of the complex impacts of aircraft noise on health and well-being. Chapter 5 of this thesis provides the first evidence of acute mortality related to night-time exposure to aircraft noise (Figure 5.1). Our findings suggest that previously measured acute biological responses to aircraft noise (e.g. high blood pressure, endothelial dysfunction) may effectively translate into acute cardiovascular mortality. This research also provides supporting evidence on the suspected importance of quiet nights in relation to cardiovascular health. Due to the large number of people exposed to night-time aircraft noise, the increased mortality associated with night-time noise exposure observed in this study is of high public health relevance.

We calculated that 3% of all-cause cardiovascular deaths in our study population could be attributed to aircraft noise, based on our categorical models (Table 5.2). In other words, 782 of the 24,886 cardiovascular deaths that occurred in the study area between 2000 and 2015 could potentially have been adverted by preventing exposure to night-time aircraft noise. This estimate makes night-time aircraft noise comparable to other triggers of cardiovascular mortality, such as strong emotions, a heavy meal, or moderate levels of air pollution (Figure 8.2). Similar estimates could be expected from other Swiss Airports (e.g. Geneva or Basel International Airport) and other European airports with a night-time flight reduction similar to Zurich Airport. Since our findings are based on night-time noise exposure only and do not include potential mortality associated to exposure to aircraft noise during the day, the calculated attributable fraction of 3% may rather underestimate the total cardiovascular health impact associated with aircraft noise.

While there is no similar study on the acute effects of transportation noise on cardiovascular mortality, our risk estimates for all-cause cardiovascular mortality (OR=1.06, 95% CI=1.00-1.13 per 10 dB increase in night-time L_{Aeq}(2h)) are comparable to previ-

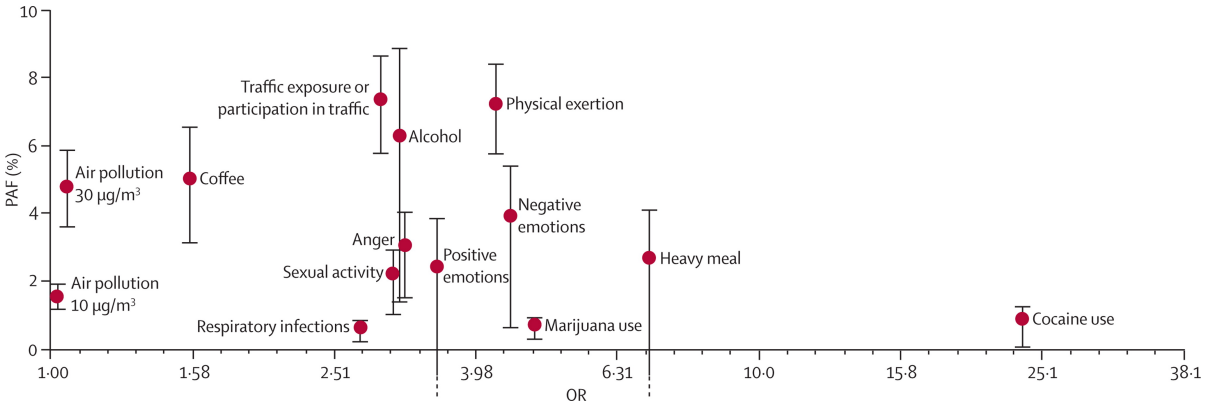

Figure 8.2: Risk of acute myocardial infarction and respective population attributable fractions (PAFs) with their respective 95% CI (error bars) for different exposures.[1]

ous research investigating the long-term effects of environmental noise on cardiovascular health. In a meta-analysis extending the WHO review [Van Kempen et al. 2018] to the most recent studies up to 2019, Vienneau and colleagues estimated the risk ratio of incidence of ischaemic heart diseases to 1.03 (95% CI = 0.98, 1.09) per 10 dB increase in L_{den} aircraft noise [Vienneau et al. 2019]. Furthermore, the cardiovascular health outcomes associated with acute night-time aircraft noise exposure are comparable to those reported on the long term. For instance, in the SNC, the highest mortality per 10 dB increase in long-term aircraft noise (L_{den}) was observed for myocardial infarction (RR=1.027, 95%CI 1.006-1.049) and heart failure (RR=1.056, 95%CI 1.028-1.085) [Héritier et al. 2017]. In line with previous long-term research [Weihofen et al. 2019; Seidler et al. 2018; Hansell et al. 2013], the risk of acute ischaemic stroke was also increased in our study (Figure 5.1), even though the sample size was rather small for this diagnosis and the results not statistically significant.

These findings are coherent with the established contribution of vascular oxidative stress as a physiological response to acute stress events. Namely, night-time aircraft noise has been proven to cause rapid increase in blood pressure and vascular dysfunction [Haralabidis et al. 2008; Schmidt et al. 2013], well-known risk factors for ischaemic heart diseases — including myocardial infarction — which we observed in our study. In contrast, heart failure has a longer onset than ischaemic diseases. While its long-

[1]Reprinted from The Lancet, Vol 377. number 9767, Nawrot, TS, Perez L, Künzli N, Munters E, and Nemery B, "Public health importance of triggers of myocardial infarction: a comparative risk assessment", Pages 732-740, Copyright (2011), with permission from Elsevier. `https://www.sciencedirect.com/journal/the-lancet`.

term association with traffic noise may be explained by noise-related hypertension — a common risk factor for the development of heart failure — if and how aircraft noise may trigger death from heart failure is less evident. It may be mediated by sleep as recently postulated by Li and colleagues [Li et al. 2020], but the exact biological mechanisms explaining the relationship between unhealthy sleep patterns and the development of heart failure still needs to be established. It cannot be excluded that adherence to healthy sleep patterns may be associated with further behaviours affecting cardiovascular health. Similarly, a diagnosis of heart failure may rather reflect the presence of specific cardiovascular risk factors, making these patients especially vulnerable to stress events such as aircraft noise events. The implication of different cardiovascular diagnoses in association with aircraft noise, temperature, and air pollution exposure will be further discussed in Section 8.4.

Considering the importance of an elevated population attributable fraction as presented in Figure 8.2 and the growing evidence on the cardiovascular health outcomes associated with aircraft noise [Haralabidis et al. 2008; Hansell et al. 2013; Schmidt et al. 2020], it is striking that the cardiovascular effects of aircraft noise are not more consistently addressed in environmental reports and burden of disease calculations [GBD Collaborators 2011; World Health Organization 2018b]. Generating and communicating scientific evidence are essential to inform environmental health policies. For instance, environmental guidelines and reports as provided by the WHO and the EEA set the ground for coordinated reporting and addressing of noise mitigation in the European region. As a result of the insufficient quality of studies on aircraft noise included in the 2018 WHO environmental noise guidelines [Van Kempen et al. 2018], cardiovascular health outcomes were not considered in the calculation of the aircraft noise levels recommendation, which was primarily based on annoyance and sleep disturbance as main outcomes. It is therefore essential to consider the cardiovascular impacts of environmental noise in general and aircraft noise in particular in future public health reports such as WHO guidelines and the Global Burden of Disease in order to adapt national policies and prevent environmental noise related deaths.

8.2 What did we learn about the timing of noise?

8.2.1 Delay between noise events and health outcomes

So far, only little was known about the potential exposure windows of importance for the acute effects of night-time aircraft noise. This thesis provides the first quantitative evidence of noise-related mortality within a short exposure window of two hours. This finding is not particularly surprising when compared to other triggering exposures such as coffee intake or physical exercise, which have also been reported to affect cardiovascular health within few hours [Nawrot et al. 2011; Rowland et al. 2020]. It is also coherent with some very short-term physiological modifications observed as a response to night-time aircraft noise, such as increased heart rate and blood pressure within 15 minutes after exposure [Haralabidis et al. 2008].

However, it remains unclear whether night-time aircraft noise can have further delayed triggering effects, beyond the investigated time-frame of two hours. Since the noise analyses were uniquely focussed on night-time exposure, a distributed lag modelling approach was not ideal. Instead, we investigated several night-time windows: (a) very acute (2h before death) for deaths occurring during the night; and (b) selected time windows in the night preceding death occurring during the day. It is hypothesized that traffic noise may have a stronger impact on sleep quality both at the beginning and the end of sleeping time [Griefahn, Marks, and Robens 2008; Röösli et al. 2019]. In contrast, the highest risk of mortality from ischaemic heart diseases in the SNC was observed for the core night hours (01:00 to 05:00) [Héritier et al. 2018]. Unfortunately, we could not confirm whether similar times of the night were of particular importance in the development of cardiovascular mortality as we did not find evidence of an effect of night-time aircraft noise lasting until the next day (Figure 5.3).

8.2.2 Exposure-response relationship: the importance of quiet phases

The exposure-response relationship observed between night-time aircraft noise and cardiovascular mortality suggests possible effects at levels below those recommended by the WHO. Furthermore, few loud aircraft noise events during the night may be sufficient to trigger cardiovascular mortality, highlighting the importance of undisturbed quiet nights.

An important challenge of this thesis was to identify the appropriate shape of the exposure-response relationship for the investigated health outcomes. To do so, I used penalized splines to model the association between short-term aircraft noise exposure and mortality with no preliminary assumption of the shape of the association. The association between L_{Aeq}(2h) and all-cause cardiovascular mortality was found to be linear, with significant increase in the OR of mortality observed from 35 dB. Thresholds were identified for some specific health outcomes, with the lowest association observed for L_{Aeq}(2h) levels as low as 30 and 50 dB for heart failure and myocardial infarction (Figure 5.1). Assuming a causal relationship, WHO's recommendations for night-time aircraft noise of 40 dB [World Health Organization 2018b], would not be sufficient to prevent the totality of the cardiovascular deaths reported here.

In the case of rare flight events and long periods of silence — as it is typically the case for night-time aircraft noise — the low thresholds reported above can represent one single or very few loud events (Appendix B, Figure S6) suggesting that few loud aircraft noise events during the night may be sufficient to trigger cardiovascular mortality, also at 2h-average levels below the recommended 40 dB. Seidler and colleagues also reported an increased risk of ischaemic heart diseases and heart failure associated with a few loud events, even at low L_{den} levels [Seidler et al. 2016]. Similarly, the introduction of the night-time curfew at Frankfurt airport reduced the overall number of awakenings, but the probability of awakening from single aircrafts remained unchanged [Elmenhorst et al. 2017]. It seems particularly important for quiet phases to remain uninterrupted, which is only possible if night-time flight restrictions are properly enforced and efforts are made to limit the number of emergency flights.

Given the importance of even few flight events as described above, it could be expected for event-based metrics to be the most relevant to predict night-time cardiovascular mortality. Interestingly, a combination of L_{Aeq} and (NAT_{55}) did not further improve the model from simple continuous exposure metric when considering all-cause cardiovascular mortality. It is possible that a few loud events may have still been captured by the main exposure window of 2h while they would have been masked in a larger exposure window. Nevertheless, NAT_{55} seemed to be best at capturing the association between 2h aircraft noise exposure and mortality from heart failure (Appendix B, Table S1). This observation is in line with a recent randomized control trial showing that the number of events is especially important on diastolic cardiac function — particularly relevant for heart failure — but not necessarily on vascular function — particularly rel-

evant for ischaemic events — which in contrast was mostly associated with night-time L_{eq} [Schmidt et al. 2020]. This finding also supports our use of L_{Aeq} as main exposure metric when investigating all-cause and ischaemic cardiovascular mortality associated with night-time aircraft noise.

Our findings in relation to noise exposure during night hours support the suspected mediation role of sleep in the association between aircraft noise and cardiovascular mortality. Sleep is characterized by lower heart rate and blood pressure, induced by a reduced sympathetic tone, which is essential for regeneration of the heart functions [Sayk et al. 2007]. In addition, the importance of sleep has been established in various noise-induced stress responses such as vascular and endothelial functions [Kröller-Schön et al. 2018; Schmidt et al. 2020], metabolism disruption [Grandner et al. 2012] and increased blood pressure [Schmidt et al. 2015], which are all risk factors for cardiovascular health outcomes associated with night-time aircraft noise as presented in Chapter 5. Similar analyses focussing on acute cardiovascular mortality associated with both night-time and day-time exposures could strengthen the current evidence on the particular importance of sleep as a mediator for the health effects associated with night-time aircraft noise, also in the development of acute cardiovascular mortality.

8.2.3 What does it mean for future policies?

Many airports across the world operate flights at all times of the day and night, exposing large numbers of people to night-time aircraft noise. If the risk estimates presented in Chapter 5 were to be confirmed in other settings with varying noise exposure levels, the logical consequence would be a generalization of night-time flight restrictions to prevent adverse cardiovascular health outcomes. In Europe, such limitations of air traffic have already been proven efficient to reduce sleep disturbance [Elmenhorst et al. 2017]. Further research on the role of individual sleeping patterns on cardiovascular health outcomes may help identify the most important times of the night to be targeted by flight restrictions [Griefahn, Marks, and Robens 2008].

It is clear that the structural and temporal characteristics of noise play an important role in their impact on human health. These particularities are for instance apparent in the different effects observed for different noise sources, as reflected in the WHO's source-specific environmental noise guidelines [World Health Organization 2018b]. However metrics such as L_{den} or L_{night} are currently used to characterize and regulate noise levels,

regardless of the exposure source and health outcome of interest. These metrics may not be suited to regulate intermittent sources of noise such as aircraft noise, especially during the night, as low average levels can mask few loud single noise events. This is particularly relevant for health outcomes where few noise events may be exceedingly important, such as heart failure and sleep quality. In contrast, event-based metrics such as L_{max} and NAT can present interesting alternatives to regulate noise levels during the night and better prevent sleep disruption and protect cardiovascular health. As one size does not fit all, alternative environmental noise guidelines combining both types of metrics (average and event-based) could be used to adequately represent the different health effects associated with different noise sources and timings, and thus prevent a wider range of adverse health outcomes.

8.3 Aircraft noise, temperature, and air pollution: the reality of multiple exposures

Most of the time, environmental exposures and their effects on health are investigated individually. This thesis provides a comprehensive overview of the individual and combined effects of aircraft noise, temperature, and air pollution on cardiovascular mortality. It therefore contributes to a broader understanding of close to real-life multiple exposures situations, relevant to tackle future public health challenges associated with increasing air traffic. In addition, this multiple exposures approach supports the validity of the individual findings reported for each exposure of interest, all the analyses being fully adjusted for the other considered environmental exposures with high spatial resolution.

8.3.1 NO_2 or $PM_{2.5}$?

Next to its focus on aircraft noise, the study setting near Zurich airport used throughout this thesis was particularly well suited to investigate the health effects associated with air pollution. Air traffic is likely to affect both air pollution levels and composition, including increased levels of ultra-fine particles (UFP) [Rivas et al. 2020; Habre et al. 2018]. While both NO_2 and $PM_{2.5}$ were individually associated with increased cardiovascular mortality, the multi-pollutant models presented in Chapter 7 showed that the association between $PM_{2.5}$ and cardiovascular mortality (all causes) was largely confounded by NO_2 levels (Table 7.3), suggesting that most of the air pollution-related

cardiovascular mortality may be attributable to NO_2. Our findings contrast with the well-established evidence of the causal action of particulate matter on respiratory health and acute cardiovascular mortality [EPA., U.S. 2019; Schwartz et al. 2015]. However, only few studies investigated the mutual confounding of NO_2 and $PM_{2.5}$ on cause-specific cardiovascular mortality. Our findings suggest that contrary to all-cause and respiratory mortality, NO_2 or associated co-pollutants may play a more important role on cardiovascular mortality than particulate matter. Therefore, the contribution of NO_2 could have been underestimated in previous research and wrongly attributed to particulate matter. NO_2 being a good predictor for traffic emissions [Bourdrel et al. 2017], it should be clarified whether a causal relationship indeed exists between NO_2 and acute cardiovascular mortality, or if these findings may rather reflect the effect of further unmeasured vehicle emission particles (e.g. volatile organic compounds) [Brook et al. 2007], or even air-traffic-related UFP [Hudda et al. 2020].

Unfortunately, precise UFP data was not available for this study. Further investigation should also complement the rather scarce available evidence on the biological effects of NO_2 on the cardiovascular system [EPA., U.S. 2016]. In addition, applying multi-pollutant approaches including $PM_{2.5}$, NO_2, and UFP would be helpful to confirm or refine the potential confounding of the association between particulate matter and cardiovascular mortality reported in this thesis. Finally, similar research could be reproduced in different settings varying in their proximity to airports, to distinguish the contribution of road and air traffic and associated pollutant mixtures on cardiovascular health outcomes. Considering the constant increase in air traffic and the resulting population exposed to both aircraft noise and air pollution, a better understanding of the individual effects of different air pollutants and their relation to airports is crucial to take the most appropriate measures to mitigate cardiovascular mortality in populations living near major airports.

8.3.2 Single or multiple exposures?

Typically, communities living close to a major airport are confronted to the combination of several environmental exposures and sometimes even complex pollutant mixtures (Figure 8.1). Multiple exposures models are useful to better capture the complexity of real-life situations and to investigate the health effects associated with combined environmental exposures.

Correlation between explanatory variables is usually the major limiting factor in the creation of multiple exposures models [Stafoggia et al. 2019]. In this thesis, the only exposures showing too much correlation to be analysed in a single model were the different temperature metrics, as well as individual exposures at different lags (Appendix D, Supplementary Figure 1). In the first case, only Tmean was included in the main models and Tmin and Tmax were used for sensitivity analyses. In the last case, the distributed (non-linear) lag modelling approach allowed to overcome the correlation issue [Gasparrini, Armstrong, and Kenward 2010].

Nevertheless, single pollutant models were still useful to specify the exposure-response relationship and to identify the most appropriate metrics and exposure windows to be included in the multiple exposures models as presented in Chapter 7. As a result, this approach allowed the calculation of unbiased estimates of the association between each considered environmental exposure and cause-specific cardiovascular mortality. The models developed in this thesis were based on four main acute environmental exposures, namely aircraft noise, temperature, NO_2, and $PM_{2.5}$. Including additional exposures (e.g. more detailed air pollutant mixtures) may be useful to represent even more adequately real-life exposure situations but usually requires specific modelling approaches due to high correlation between the exposure variables of interest [Stafoggia et al. 2019].

8.3.3 Confounding in multiple exposures models

Environmental noise is only rarely included in studies investigating the health effects of air pollution and temperature. Furthermore, it has recently been suggested that research on aircraft noise may be confounded by air traffic related pollution [Hudda et al. 2020]. Except for NO_2 and $PM_{2.5}$ as described above, there was only little mutual confounding between the different exposures considered in this study. For instance, the association between night-time aircraft noise and cardiovascular mortality was not confounded by air pollution or temperature. Similarly, the results from aircraft noise, temperature, and NO_2 were robust and the risk estimates were only marginally affected by adjusting for other environmental exposures (Table 7.2). These results support the validity of existing single-pollutant models when investigating the acute effects of temperature on cardiovascular mortality. Nevertheless, including noise exposure in health analyses could improve the quality and precision of the risk estimates. In addition, the multiple exposures approach used throughout this thesis made it possible to identify possible interactions (e.g. between heat and particulate matter for the risk of heart failure

and suggestive between cold and NO_2 for myocardial infarction, see Figure 6.2). Because different exposures involve different physiological pathways, they are likely to present varying individual and combined effects depending on the health outcome of interest, as described in Section 8.4. Therefore, a multiple exposure approach as developed in this thesis is important to improve the general understanding of real-life combined exposures on specific health outcomes.

8.4 Different exposures, different health outcomes?

Given the heterogeneity of pathologies grouped as 'cardiovascular diseases', a cause-specific approach is useful to disentangle the role of environmental exposures on different health outcomes. Comparing the individual effects of various environmental exposures on specific causes of cardiovascular deaths within the same study population, I assessed their contribution to different health outcomes, in the light of their underlying physiological mechanisms. These insights are important to support the supposed way of action from environmental exposures on acute mortality, and to help tailor prevention measures to the most susceptible groups of the population.

8.4.1 Ischaemic heart diseases

Both aircraft noise and heat-related mortality were particularly pronounced for ischaemic events, including ischaemic heart diseases, myocardial infarction, and suggestive for ischaemic stroke. The occurrence of ischaemic events can easily be explained by noise-induced stress response with increased sympathetic tone and by the natural physiological response to heat. In case of a heat event, the normal physiological response includes the regulation of body temperature through an increase of the peripheral circulation, via a combination of vasodilatation and increased heart rate. The combination of a higher cardiac demand and reduction of central pressure can lead to an insufficient oxygen supply to the heart muscle and to the brain. In association with NO_2, the risk of myocardial infarction was also increased for cold temperatures, possibly due to cold-related vasoconstriction worsened by additional stress on the heart function in association with NO_2.

Acute air pollution and especially NO_2 exposure also increased the risk of ischaemic cardiovascular diseases. In this case, the risk of mortality could rather be explained by local inflammation and resulting increased blood pressure, coagulability, and increased

plaque instability [Du et al. 2016], even though the exact biological action of NO_2 on the cardiovascular function is still unclear [EPA., U.S. 2016]. Whether acute cardiovascular mortality is directly attributable to NO_2 or to further combustion-related co-pollutants, aircraft noise and air pollution are suspected to share some physiological responses (e.g. vasoconstriction, increased blood pressure), characterized by vascular-oxidative stress and cardiac activation, risk factors for ischaemic heart diseases [Bourdrel et al. 2017].

8.4.2 Ischaemic and haemorrhagic stroke

Similar to long-term studies [Héritier et al. 2017; Weihofen et al. 2019], our findings on aircraft noise were also suggestive of an increased risk in cardiovascular mortality from ischaemic but not haemorrhagic stroke (Figure 5.2), supporting different physiological mechanisms behind these two disease groups. Moreover, increased coagulability and plaque instability associated with air pollution exposure further explains the particularly strong association observed between this exposure and ischaemic stroke [Du et al. 2016]. As suggested by Weihofen and colleagues [Weihofen et al. 2019], environmental health research should distinguish between these two groups of diseases, since combining them may lead to an underestimation of the overall risk estimates.

8.4.3 Arrhythmia

The risk of cardiovascular mortality by arrhythmia was especially pronounced in association with acute exposure to night-time aircraft noise despite a rather small sample size (only 6% of all cardiovascular deaths, Table 5.1) but was not significantly increased in association with any of the other investigated environmental exposures. Arrhythmias covers a wide range of diseases, going from conduction disorders to sudden cardiac arrest, all characterized by an impairment of the normal cardiac rhythm. Next to the common pre-existing cardiovascular risk factors and existing cardiac pathologies (e.g. valve disorders), high blood pressure, stress and sleep apnoea are known to increase the risk of arrhythmias in susceptible patients [Ludka, Konecny, and Somers 2011]. These risk factors share some common pathways with acute response to night-time noise (e.g. acute stress response and increased blood pressure), possibly explaining the findings presented in Chapter 5. The similarities between night-time aircraft noise and sleep apnoea are particularly striking, both involving sleep disruption and a perturbation of the normally reduced blood pressure and heart rate during sleeping phases.

8.4.4 Heart failure

The risk of heart failure behaved differently across the different exposures and lag periods investigated in this thesis. A risk increase was already observed at relatively low levels of 2h-nighttime aircraft exposure (30 dB L_{Aeq}, 5 NAT_{55}), possibly explained by stress-induced high blood pressure and potential impairment of the diastolic function [Schmidt et al. 2020]. In contrast, for heat-related mortality, heart failure was observed only in combination with air pollution and with a delayed lag-response curve compared to the other heath outcomes, with the higher OR at lag days 3 to 5, following an initial risk reduction at lags 0-3 (Figure 7.1). Reduced vascular resistance and volume depletion as a physiological response to heat events may explain this initial risk reduction. Furthermore, the higher demand in terms of heart rate together with an increase stress due to air pollution could explain the delayed increased risk of heart failure, after normalization of the vascular response.

8.4.5 Hypertensive heart diseases

Only temperature seemed to affect the risk of hypertensive mortality. While this outcome is coherent with a response to cold [Fares 2013], it may at first seem counter-intuitive as a response to heat, characterized by a reduction of the central pressure. In a similar study, [Ragettli, Schulte, and Röösli 2021] also found an increased risk of mortality but a reduced number of hospitalizations for hypertensive heart diseases associated with heat events and postulated that this finding may be the result of blood-pressure-reducing medication in hypertensive patients, which reduces their coping capacity to heat-induced hypotension. This explanation is coherent with our results and with the possibility that some cause of death coding may rather reflect underlying pathologies than the exact trigger of death [Zellweger et al. 2019].

8.5 Environmental exposures across the life course: a contribution to environmental health equity

By comparing the vulnerability to different environmental exposures within the same study population, I gained understanding on how some groups of the population are differently affected by their environment. In addition to environmental pollution being unequally distributed across the population, I found that socially and economically

deprived population groups also presented an increased susceptibility to develop adverse health outcomes as a response to these exposures. Finally, I postulate that the differences in exposure and susceptibility observed across the different exposures may be explained by housing, physiological, and behavioural mechanisms. These findings can inform future health policies and urban planning measures to reduce environmental health inequity in Switzerland.

8.5.1 Individual vulnerability to environmental exposures

In Section 8.4, I highlighted the similarities between aircraft noise and air pollution related mortality with regards to their shared biological mechanisms in the development of ischaemic heart diseases. However, these two groups of exposures differed in relation to identified vulnerable groups. For instance, in Chapters 5 and 6, I found that females, older people, and less privileged groups of the population (e.g. lower education, socio-economic position) were at higher risk of acute cardiovascular mortality associated with aircraft noise and heat. In contrast, individual and social characteristics did not consistently modify the susceptibility to air pollution exposure. The groups of the population identified as most susceptible in relation to NO_2 exposure varied between health outcomes, likely to reflect differential risk factors associated with cause-specific mortality in these groups.

The reason why individual characteristics such as lower socio-economic position may affect the acute response to aircraft noise and heat but not air pollution may be related to the ability to avoid or cope with a certain exposure. For instance, in the case of a heat-wave, beyond the individual capacity of the body to regulate the temperature, behaviours such as staying at home and drinking enough water can drastically improve one's ability to cope with the heat. Social deprivation or low health literacy can also affect the adherence to such prevention measures [World Health Organization 2010]. Similarly, less privileged groups may have limited ability to escape the heat (e.g. air conditioning, retreat to the mountains), which can explain the observed increased vulnerability in our study. In the case of air-pollution, similar adaptations are typically not possible, explaining the homogenous response across population subgroups for all-cause cardiovascular mortality. However, the exposure to NO_2 and $PM_{2.5}$ were consistently increased for low socio-economic groups (Table 7.1), still setting this part of the population at higher absolute risk of air pollution related mortality (a similar distribution table of transportation noise across subgroups of the study population is included in Appendix

F). While night-time aircraft noise cannot be escaped like heat, lower socio-economic position may be associated with lower noise insulation or simply a worsened general health status, leading to an increased susceptibility to vascular stress events. Being married is typically considered to be a protective factor for all-cause mortality [Staehelin et al. 2012] and was found protective for heat and aircraft noise related mortality in this research. This protective effect can be associated with lifestyle and behavioural differences. In contrast, not being married was also associated with older age and may be an indicator of social isolation in our study.

Beyond behavioural and other coping mechanisms, the differential distribution of health outcomes across socioeconomic positions and between genders may further explain the cause and gender-specific results presented above. Figure 8.3 shows that ischaemic heart diseases affect males with higher socio-economic position in a larger proportion. In contrast, females — especially from lower socio-economic position — suffer exceedingly from cerebrovascular diseases and 'other cardiovascular and circulatory diseases'. This last group covers a wide range of diseases and includes arrhythmias, which were especially important in acute aircraft noise associated mortality and could explain the stronger effect observed in women in Chapter 5.

More generally, high vulnerability groups shared most characteristics in relation to acute aircraft noise and heat-related mortality: regardless of the indicator, the oldest and the least privileged groups of the population were found to be the most vulnerable. For instance, older age groups were particularly susceptible to develop adverse cardiovascular health outcomes in relation to aircraft noise and heat. The effect modification by education (especially for females) was also consistently observed throughout these two exposures. Effect modification by socio-economic position was not consistent throughout genders and exposures, as often reported in previous studies [Murage et al. 2020]. It is generally complicated to compare stratified results of socio-economic position across study sites, as the definition of socio-economic position is rather heterogeneous between studies and may reflect different underlying individual characteristics [Murage et al. 2020]. Overall, the gender-differential distribution of cardiovascular diseases along the socio-economic index presented in Figure 8.3 can explain why lower education and socio-economic position was especially relevant for females in our study. For males, the increased risk observed for heat-related mortality at higher socio-economic position described in Chapter 6 may rather be associated with differences in lifestyle and behaviour, as reflected in Figure 8.3. Similarly, the differences in susceptibility across different causes

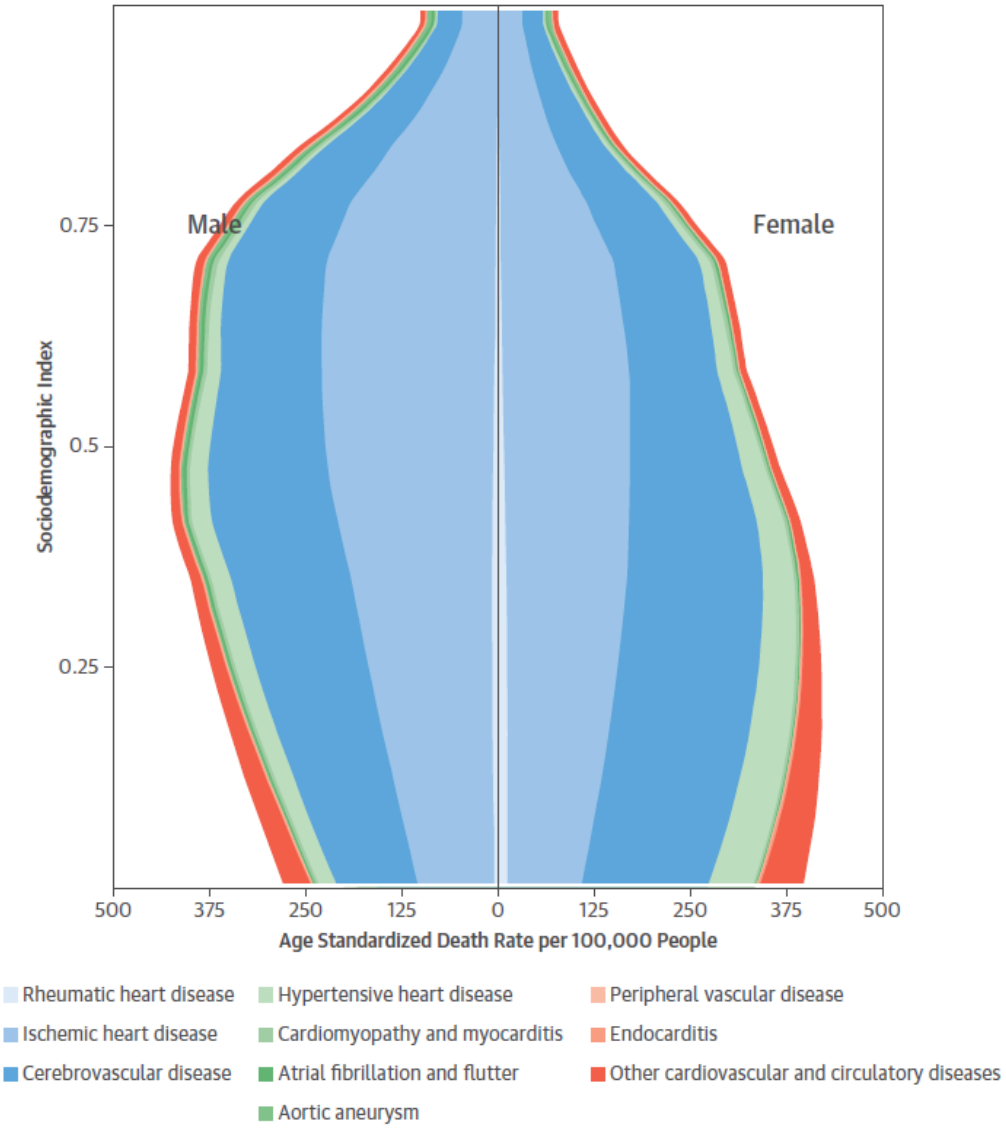

Figure 8.3: Relationship Between Age-Standardized Mortality Rate, CVD Cause, and socio-demographic index, by sex. The socio-demographic index ranges from 0 (lowest) to 1 (highest). Reproduced from [Roth et al. 2017].

of death observed in relation to NO_2 exposure support the possible uneven distribution of certain risk factors in some groups of the population, explaining increased relative risks for specific health outcomes. For example, the relative risk of mortality from ischaemic stroke was increased for younger males (Table 7.4), likely to spend more time outdoors or to be exposed to air pollution at work or while commuting. However, while the relative risks were increased for the younger population in association with NO_2, the

absolute risk of mortality remained highest for the older age groups (mean age at death = 80 years old).

In the case of aircraft noise, current evidence is rather heterogeneous regarding gender differential susceptibility. For instance, long-term exposure to transportation noise is typically associated with increased relative risk of ischaemic heart diseases for males and metabolic disorders for females [Eriksson et al. 2014; Pyko et al. 2015]. In Chapter 5, we report an increased susceptibility to acute aircraft noise for women. While these results contrast with previous research on the long-term exposure to transportation noise [Héritier et al. 2017; Vienneau et al. 2015], women have been reported to present an increased acute stress response after exposure to traffic noise (i.e. increase in saliva cortisol) [Paris et al. 2010; Selander et al. 2009], which supports the increased relative risk of cardiovascular mortality for women observed in Chapter 5. Post-menopausal status is another possible explanation for the gender differences observed in this thesis but could not be confirmed due to insufficient data on younger age (mean age = 84 years old, 1.3% of females below 55 years old).

The plausibility of these findings was further supported by the stronger effect observed in locations with reduced background noise levels, where noise events may be more audible. Aircraft noise and heat-related mortality was also found to be highest for people living in older buildings, likely to be less insulated. However, this difference is likely to be — at least partially — driven by socio-economic position, which was generally lower for people living in older buildings (Table 8.1). For instance, environmental noise may affect property prices, and therefore be associated with socio-economic position or specific individual and lifestyle characteristics [Münzel et al. 2018]. However, these differences may also vary across neighbourhoods. For instance, older building in historic city centres may, on the contrary, be more desirable and associated with higher socio-economic position. Further adjusting for renovation status did not give consistent results across environmental exposures, likely to reflect further unmeasured individual characteristics than insulation status. Finally, health response to environmental exposures may further vary across different cultural, climatic and language regions, not fully captured in this study.

Table 8.1: Distribution of socio-economic position levels (percentiles SSEP) across different types of buildings (building period).

	Socio-economic position (SSEP)		
Building period	25^{th} percentile	median	75^{th} percentile
before 1970	60.7	67.2	73.2
1970-1990	60.9	68.6	74.7
after 1990	63.9	70.5	75.5

Kruskall-Wallis test, $p<0.01$

8.5.2 The role of the living environment

In section 8.5.1, I described how behaviour, but also the direct environment and living conditions can explain differences in exposure and susceptibility to air pollution, heat, and transportation noise. As a result, the following actions could be derived to promote cardiovascular health with regards to the environment: (1) reducing the exposure levels at the source; (2) promoting adequate response to environmental hazards and heat events; and (3) mitigation measures such as improved heat and noise insulation, increasing the urban greenness (not specifically studied in this thesis). In all cases, it is crucial to ensure that such actions specifically benefit to the most vulnerable groups of the population, namely the elderly and the socially and economically deprived.

Modern urban planning is a perfect tool to jointly address and mitigate several environmental exposures at once. For instance, increasing urban greenness can positively impact heat and air pollution levels, but also noise perception and overall mortality [Baudin et al. 2020; Nieuwenhuijsen et al. 2018; Vienneau et al. 2017]. Parks and green spaces can indeed act as visual and auditory shelters, increase social cohesion, and promote physical activity. However, urban green was reported to act positively on noise sensitivity for all traffic-related noise sources, except for aircraft noise, which was exacerbated [Schäffer et al. 2020]. It remains to be proven if similar modulations of the noise perception also play a role in acute cardiovascular mortality as a response to aircraft noise. This point is particularly relevant, knowing that aircraft noise is typically responsible for higher noise annoyance than road and railway noise [Brink et al. 2019]. Yet, it is not clear whether the increased mortality observed in Chapter 5 for people living in more quiet areas is only attributable to the fact that noise events are better audible in a quiet environment or if it may also be modulated by individual perception or higher noise sensitivity. More research is needed to clarify whether sensitive people may actively move to quieter loca-

tions or if the perceived impact could be greater because the source of noise cannot be escaped.

8.6 Bias and causality in the case-crossover study design

With only few exceptions [Schmidt et al. 2020], it is typically not possible to conduct randomized control trials to investigate the health effects of environmental exposures. Therefore, the assessment of a causal pathway usually relies on observational studies. Adequate identification, measurement, and adjustment for potential confounders are therefore crucial to obtain unbiased risk estimates. Causality is a vast topic, which was not exhaustively addressed in the context of this thesis. The most important criteria to meet for causality in environmental research have been very well described in 1965 by Sir Austin Bradford Hill [Hill 1965] and are still relevant today. Among them, 'temporality' requires the exposure to happen before the outcome in order to out-rule potential reverse causality. Current evidence on the cardiovascular effects of aircraft noise, primarily based on cross-sectional studies, does not fully satisfy this criterion. Another main criticism in noise research is potential residual confounding by individual and socio-economic characteristics. In addition, some lifestyle factors have also been shown to be associated with several environmental exposures (e.g. obesity and physical activity are associated with transportation noise). Finally, adjusting for variables which are on the exposure-response pathway may further confound the association of interest [Münzel et al. 2020a].

All causality criteria cannot be fulfilled in a single study but individual studies with different strengths and weaknesses can jointly contribute to assessing causality. This thesis contributes to the generation of evidence in the field by using large cohort data in a case-crossover study design, reducing the risk of confounding by individual and social characteristics. The choice of control events both before and after the day of death (time-stratified sampling approach) further reduces the risk of bias associated with temporal trends [Janes, Sheppard, and Lumley 2005; Lumley and Levy 2000].

Other acute triggers of cardiovascular mortality (e.g. physical exercise, coffee, drug use) are not expected to be sources of systematic bias in these analyses. While they may explain part of the models' variability, they are not expected to be associated with the

environmental exposure of interest. They may therefore lead to an underestimation but no overestimation of the risk estimates.

However, due to rather low aircraft noise levels, larger uncertainty was observed in the risk estimates for the highest exposure groups. In addition, higher exposures usually occurred during more 'busy' time windows (e.g. evening and overall night, see Figure 3.5), where less variation was observed between case and control events, resulting in limited power for these exposure windows. Similarly, less variation was observed for NAT_{55}(2h) compared to L_{Aeq}(2h), possibly explaining the lower predictive power of this exposure metric. Therefore, a similar approach may have limited power if applied to day-time noise or larger exposure windows with reduced day-to-day variability.

8.7 Towards increasingly accurate individual exposures

Exposure misclassification is one of the main limitations to environmental epidemiological studies based on observational data. While the 'true' exposure does not exist — or at least cannot be simply measured — the increase in computational capacities over the past decades changed the face of environmental research. Wide administrative cohorts ensure increasing power required for refined epidemiological analyses but also rely on retrospective exposure assessment as compared to experimental studies and prospective cohorts where individual exposures are measured in real-time. The recent boom in machine learning techniques, together with the availability of large remote sensing data sources, opened a whole new world of possibilities for epidemiologists on the pursuit of the perfect exposure estimate.

8.7.1 Precise exposure metrics

Part II of this thesis was specifically dedicated to address the issue of exposure misclassification by developing an approach to calculate individual aircraft noise and NO_2 estimates with high spatial and temporal resolution for the health analyses presented in Part III. The flexibility of exposure windows and noise metrics calculated in Chapter 3 for this case-crossover study enabled to precisely identify the characteristics of aircraft noise which have the most impact on cardiovascular mortality as well as the most important exposure windows for this association. The aircraft noise calculations from chapter 3 are

specific to Zurich airport but may be applied to other settings using similar individual flights and noise calculations. The NO_2 models developed in Chapter 4 and the $PM_{2.5}$ models (existing for some years and extended in Chaper 7) at 100 × 100 m resolution are among the most precise daily air pollution exposure estimates available to this day. Next to their availability for the present study, these air pollution models can be used to extract precise air pollution estimates for future epidemiological research conducted in Switzerland.

Some exposure misclassification could not be avoided, for instance if people were not at home at the time of death or on control nights. This possibility should however be limited due to the focus of this study on night-time noise exposure, when people are more likely to be at home. Including individual sleeping patterns would be necessary to assess the role of sleep for the different cardiovascular health outcomes with more certainty. Further, the absence of address history between the 2000 and 2010 census data may result in incorrect location at the time of death. Sensitivity analyses restricted to the years 2015 to 2016 with yearly address follow-up did not modify the conclusions of this study. Finally, individual deviations from the flight paths used for the aircraft noise calculations could not be avoided. In all cases, the resulting exposure misclassification is likely to affect the overall power of the study and could lead to an underestimation of the risk estimates and should therefore limit the risk of false positive findings.

8.7.2 Capturing non-linear relationships

Many exposures present non-linear associations with different health outcomes. To quantify this association without bias, it is critical to adequately specify the shape of the exposure-response relationship. In this context, splines are very useful to model non-linear exposure-response relationships. When the shape of the association is unknown, splines also allow to investigate the shape of the association of interest and identify potential thresholds as shown in Chapter 5. However, if not specified correctly, they may introduce bias in the analysis: if too smooth, they may not represent the 'real' shape of the exposure-response relationship. If too flexible, they may result in over-fitting, as presented in Figure 8.4. To limit this risk, the number of degrees of freedom can be selected to minimize Akaike's criterion, as performed in Chapters 5 and 6. The use of penalized splines further limited any overly strong influence of the risk estimates by extreme values. Alternative strategies to model non-linear associations between two continuous variables are (i) variable grouping (e.g. age, socio-economic position); (ii)

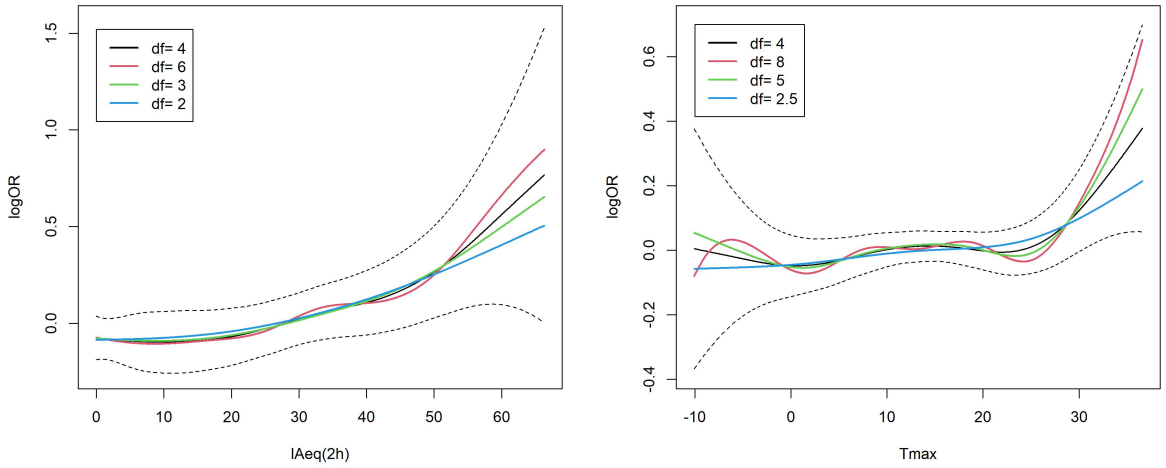

Figure 8.4: Penalized spline with varying degrees of freedom for the association between the risk of cardiovascular mortality and L_{Aeq} on the left and Tmax on the right. Increasing the number of degrees of freedom makes the curve more “wiggly" and increases the estimate difference on the extremities of the curve.

centring and modeling as a continuous variable (e.g. adult age); or (iii) using higher degree polynomials such as squared or cubic terms. This last approach is very useful when having previous knowledge of the expected shape of the exposure-response relationship. For instance, in Chapter 6, Tmean was modelled as a second degree polynomial in the confounding and effect modification analysis with air pollution.

8.8 Public health relevance and potential policy responses

This PhD thesis contributes to public health by addressing major knowledge gaps around aircraft noise and environmental epidemiology. With the rapid expansion of air traffic — the number of passengers has doubled between 2006 and 2018 [ICAO 2020] — an increasing number of people are going to be exposed to aircraft noise and pollution worldwide. Since environmental exposures usually cannot be reduced or avoided at the individual level, political and systemic public health efforts are crucial to protect the overall population’s health. The scientific evidence generated in this thesis regarding the acute cardiovascular health outcomes associated with aircraft noise and further environmental pollution can help inform health policies and reduce associated mortality and

morbidity. It also contributes to a broader understanding of the most relevant exposure characteristics and timing of aircraft noise for its association with cardiovascular mortality.

Most of the existing evidence on the health effects of aircraft noise focuses on annoyance, but little data exists on cardiovascular health, and even less on mortality [Van Kempen et al. 2018]. This thesis produced the first evidence of acute cardiovascular mortality triggered by night-time aircraft noise events. With an attributable fraction comparable to other triggers of coronary heart diseases, such as anger and coffee intake, it is particularly important to include the contribution of aircraft noise on cardiovascular health in future burden of disease calculations and environmental noise regulatory limits.

Moreover, the adverse cardiovascular health outcomes reported in this thesis are suspected to occur at levels below the recommended 40 dB L_{night}. If these findings were to be confirmed by future research, this threshold would need to be revisited. Additionally, given the importance of undisturbed quiet nights, alternative metrics taking into account the maximum event levels such as L_{Amax} and number above threshold should be considered for the generation of new noise regulatory limits to reduce sleep disturbances and prevent excess cardiovascular mortality in populations living around major airports. Similarly, source-specific regulations should be more systematically promoted to address differential health responses associated with different sources of transportation noise.

These findings set the foundation for further research aiming at refining the current evidence on the delayed response to acute noise events. In particular, identifying the adequate timing for night-time flight curfews taking into account the most relevant exposure windows and individual sleeping patterns can positively improve the benefits of such measures on cardiovascular health outcomes [Griefahn, Marks, and Robens 2008].

This thesis focussed on several sources of environmental exposures, which are interlinked in the context of a changing climate. Beyond mere recommendations in aircraft noise levels mitigation, effort should be made to consider the mutual benefits of urban planning interventions on several exposures and their global gain for health. For instance, road traffic noise and annoyance can be reduced by the creation of parks and green spaces [Schäffer et al. 2020], which are also beneficial for mental health, can encourage physical exercise [James et al. 2017], and may also help prevent heat-related mortality due to cooling performance [Richards et al. 2020]. The city of Lausanne in

Switzerland recently aimed to combine several beneficial health outcomes as the result of a single public health measure by limiting road traffic speed to 30 km/h during the night. This single intervention contributed to reducing both night-time noise levels and morbidity due to road accidents [Rossi et al. 2020]. While such actions provide less protection in the case of aircraft noise, efforts can be made to limit noise at its source by introducing less noisy aircraft, optimizing approach and landing trajectories, and implementing air traffic limitations [ICAO 2020]. Further mitigation measures to limit perceived aircraft noise can be achieved by locally improving noise insulation and applying appropriate zoning and urban planning.

While the research presented in Chapter 7 is not sufficient to fully disentangle the individual contributions of air traffic related pollution, it supports the un-confounded association between aircraft noise and acute cardiovascular mortality. It also highlights the particularity of a population located in the vicinity of a major airport in terms of air pollution levels and mixtures. This work should encourage future research to further investigate the individual contributions of traffic-related pollutants, such as NO_2, UFP, and volatile organic compounds often disregarded and potentially relevant in the light of increasing urbanization and air traffic.

In summary, there are many policy responses that have been shown to reduce the environmental burden of disease. However, they require long-term planning and political will for effective implementation. The different environmental exposures studied in this thesis and selected possible mitigation measures are presented in Figure 8.1.

8.9 Outlook

Environmental epidemiology proves its value in the context of a quickly evolving environment and when new, as of now unknown problems have to be faced. In doing so, it is essential to always consider health equity. Recent global sanitary crises indeed proved that while public health measures are key for change, they often come at a social and economic cost. For instance, in the context of the current coronavirus pandemic, lock-down measures needed to limit the spread of the disease disproportionally affected the most vulnerable parts of the population, such as older people and those with lower job stability [United Nations 2020b]. Unequal distribution of environmental exposures are the cause of health inequity around the globe, some social, ethnic, and education groups being systematically exposed to higher noise and pollution levels than the rest

of the population [Dreger et al. 2019; Fairburn et al. 2019]. Additional to being increasingly exposed, these same groups are often also more susceptible to developing adverse health outcomes as a response to these environmental exposures, further increasing their absolute risk of mortality and morbidity. This thesis showed that many characteristics were shared for vulnerability to aircraft noise and temperature-related mortality. Where developing countries face the 'double burden of disease', referring to the burden of both infectious and non-communicable diseases, in many Western countries, part of the population is exposed to a multiple burden of adverse environmental exposures and health outcomes. To address this issue, future public health measures should set particular emphasis on protecting the most vulnerable groups of the population, namely the elderly, and the most socially and economically deprived.

Environmental actions are often seen as an opposition to progress and economic growth. However, several initiatives have proven that both can co-exist and that environment and health-friendly actions can even sustain the economy [World Health Organization 2020]. A comprehensive consideration of the living environment is needed to efficiently address environmental pollution and promote good health. Such efforts have already started with the development of multiple-pollutant approaches [Stafoggia et al. 2019], the creation of the exposome concept [Wild 2012; Daiber et al. 2019], and further programmes promoting a global vision of equitable urbanization and environmental health [United Nations 2020a]. While infectious diseases have dominated the public health advances in the previous century, improving environmental health will play a major role in the improvement of global health in the future to promote sustainable, healthy, and equitable communities.

8.10 Conclusion

The aim of this thesis was to understand the role of night-time aircraft noise on cardiovascular mortality. Based on a robust study design and precise environmental exposures calculated at home location for 24,886 cases of cardiovascular deaths around Zurich airport, this thesis provides the first evidence of acute cardiovascular mortality triggered by short-term exposure to aircraft noise during the night hours. The evidence generated through this research should be conceived as a contribution to further understand the short-term impacts and the timing of aircraft noise. It contributes to the rising awareness of the health benefits from noise reduction and undisturbed sleep and

supports the independent associations of aircraft noise, but also extreme temperature and air pollution, with acute cardiovascular mortality. Finally, it shows that individual, social, and behavioural characteristics are particularly important for the physiological response to environmental exposures. The most deprived groups of the population tend to be at higher exposure to environmental pollution, and are often also more susceptible to develop adverse health outcomes.

Air travel will continue to be an important driver of development and economic growth. The results presented in this thesis underline the importance to address the public health impacts of aircraft noise at a policy-level. In light of the limited policy responses towards noise reduction, it is crucial to raise awareness and increase political efforts to protect the health of the many that are exposed to aircraft noise on a daily basis. Infrastructures and urban planning, as well as mitigation measures should be integrated in a comprehensive approach to improve environmental health. This thesis also emphasizes the need to tailor and target future environmental and health policies to vulnerable groups to move towards environmental health equity.

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Part V

Appendices

Appendix A: Supplementary materials from Chapter 4

Predicting Fine-Scale Daily NO2 for 2005-2016 Incorporating OMI Satellite Data Across Switzerland

Kees de Hoogh[1,2], Apolline Saucy[1,2], Alexandra Shtein[3], Joel Schwartz[4], Erin A. West[5], Alexandra Strassmann[5], Milo Puhan[5], Martin Röösli[1,2], Massimo Stafoggia[6], and Itai Kloog[3]

[1] Swiss Tropical and Public Health Institute (Swiss TPH), Basel, Switzerland
[2] University of Basel, Basel, Switzerland
[3] Ben-Gurion University of the Negev, Beer Sheva, Israel
[4] Department of Environmental Health, Harvard T. H. Chan School of Public Health, Cambridge, United States
[5] Epidemiology, Biostatistics and Prevention Institute, University of Zurich, 8001 Zurich, Switzerland
[6] Department of Epidemiology, Lazio Regional Health Service,Rome, Italy

Materials and Methods

1. Global and local predictor variables

Emissions; NOx emissions for the years 2005, 2010 and 2016 were obtained from Meteotest at a 200x200m grid, covering agriculture, household, industry, traffic and wood smoke emissions. For traffic, emission data was modelled using information about the Swiss road network, traffic intensity from the Swiss national traffic model and national emission factors. Industrial emissions were calculated by summing the stationary sources from NFR categories 1A1 "Energy Industries", 1A2 "Manufacturing Industries and Construction", 2 "Industrial Processes" plus emissions from crematories. Agricultural, household and wood smoke emissions were obtained from the Swiss Federal Office of Environment (FOEN) and were distributed across the relevant land uses.

Roads; length of major and all roads were extracted from TeleAtlas MultiNet TM.

Traffic intensity; Traffic intensity was obtained from the Sonbase 2010 database. Before intersecting with the 100x100m polygons, tunnels were removed from the road shape file. Traffic intensity, calculated as the daily traffic volume times road length was rasterised and using focalsum turned into 100, 200, 300, 1000, 2000, 5000 and 10000m buffers.

Elevation; we use the digital height model DHM25 at a 200m grid, based on the Swiss National Map 1:25 000 (Source: Swiss Federal Office of Topography). Average errors, when comparing model heights with measurements, are between 1.5 and 8m depending on the region.

Intersections; Road intersections were obtained from the Sonbase 2010 database and were defined as a node we 3 or more roads connect. The number of intersection were calculated for each 100x100m cell and using focalsum turned into 100m, 150m and 250m buffers

Land Use; the 100x100m European Corine Land Cover (CLC2006) data set was obtained. From the 44 land classes available in Corine, six main groups were extracted: residential (Corine class = 1 + 2; RES), industry or commercial (3; IND), urban green (10; URBGR), total built up (1-9; BUILT), agriculture (12 - 22; AGR) and semi-natural and forest (23 - 41; NAT). The percentage of each land use variable within each grid cell was calculated.

Light-at-Night; The 2015 Visible Infrared Imaging Radiometer Suite (VIIRS) Nighttime Lights Annual Composite at a 750x750m spatial resolution was obtained from the U.S. National Oceanic and Atmosphere Administration (NOAA) website (https://www.ngdc.noaa.gov/eog/viirs/download_dnb_composites.html) and is generated by the Earth Observation Group, NOAA National Geophysical Data Centre. This data product was cleaned prior to averaging by removing stray light, lightning, lunar illumination and cloud-cover.

Meteorology; daily modelled planetary boundary layer data, daily temperature, wind speed, wind direction and precipitation at a ~10x10km resolution from 1 January 2005 till 31 December 2016 were obtained from the European Centre for Medium-Range Weather Forecasts (ECMWF). The meteorological variables are modelled through the ERA-Interim, the global atmospheric re-analysis [19]. The temperature variable was converted from Kelvin to degrees Celsius. Wind speed (ws) and wind direction (wd) at 10 metres was calculated from the U_{10} and v_{10} components using the formulas:

$$wd = atan2\left(-u_{10}, -v_{10}\right) x \frac{\pi}{180}$$

$$ws = \sqrt{{u_{10}}^2 + {v_{10}}^2}$$

NDVI; A 30x30m raster depicting the Normalised Difference Vegetation Index (NDVI) was derived by combining 6 tiles, covering the extent of Switzerland, downloaded from the USGS EarthExplorer website (http://earthexplorer.usgs.gov). The tiles were taken with the LANDSAT 8 satellite between 8 June and 19 July 2014 without any cloud cover

Coordinates; X and Y coordinates were extracted on the basis of centroids from the grid cells

Table S1: Summary statistics for number of daily NO_2 observations, sites and measured NO_2 concentrations used in the stage 1 modelling.

Year	Number of unique NO_2 sites	Number daily NO_2 observations	25th percentile NO_2 concentration ($\mu g/m^3$)	Mean NO_2 concentration ($\mu g/m^3$)	75th percentile NO_2 concentration ($\mu g/m^3$)
2005	67	23958	15.07	27.55	37.47
2006	83	29749	14.05	27.56	37.56
2007	97	33686	13.61	26.33	36.04
2008	105	38087	13.54	26.48	36.63
2009	108	38960	13.13	26.09	35.81
2010	108	38970	13.50	26.44	36.16
2011	107	38583	13.28	26.36	36.50
2012	106	38697	12.22	25.03	34.27
2013	108	38617	12.79	25.64	35.23
2014	110	38664	12.26	24.09	33.12
2015	106	36821	12.00	25.08	35.20
2016	110	38229	11.20	23.16	32.40

Table S2: Predictor variables with defined buffer sizes, a priori defined direction of effect, and indicator at what scales they were used.

GIS Dataset	Predictor variable	Buffer size (in metre)	Direction of effect	Scale(s)[1]
Road network	Length of major roads	NA	+	1, 2
	Length of all roads	NA	+	1, 2
	Intersections	100, 150, 250	+	3
Traffic intensity	Daily traffic volume times road length	100, 200, 500, 1000, 2000, 5000, 10000	+	3
CORINE	Percentage of total built up area	NA	+	1, 2
CORINE	Percentage of residential area	100, 200, 500, 1000, 2000, 5000, 10000	+	3
	Percentage of industrial and commercial area	100, 200, 500, 1000, 2000, 5000, 10000	+	3
	Percentage of total built up area	100, 200, 500, 1000, 2000, 5000, 10000	+	3
	Percentage of urban green area	100, 200, 500, 1000, 2000, 5000, 10000	-	3
	Percentage of natural area	100, 200, 500, 1000, 2000, 5000, 10000	-	3
VIIRS	Light at night	NA	+	3
NDVI	Greenness	NA	-	3
NOx emissions	Agricultural	NA	+	3
	Household	NA	+	3
	Industry	NA	+	3
	Traffic	NA	+	3
	Wood smoke	NA	+	3
Coordinates	X, Y	NA	+/-	1, 2, 3
Altitude	Mean altitude	NA	-	1, 2, 3
Meteorology	Boundary layer height	NA	-	1, 2 ,3
	2 metre temperature	NA	+/-	1, 2 ,3
	Wind direction	NA	+/-	1, 2 ,3
	Wind speed	NA	-	1, 2 ,3
	Total cloud cover	NA	+/-	1, 2 ,3
	Total precipitation	NA	-	

1) Scales: 1 = 13x24 km; 2 = 1x1 km; 3 = 100x100 m

Table S3: Mean (and standard deviation) NO_2 concentrations ($\mu g/m^3$) per weekday for the full NO_2 monitoring dataset (2005 – 2016).

Weekday	Number of observations	Mean NO_2 concentration	Std. Deviation
Sunday	65209	18.77	12.89
Monday	65329	26.06	16.28
Tuesday	65274	27.76	17.00
Wednesday	65292	28.23	17.09
Thursday	65385	28.47	17.23
Friday	65447	28.26	17.15
Saturday	65393	23.07	14.83
Total	457329	25.80	16.49

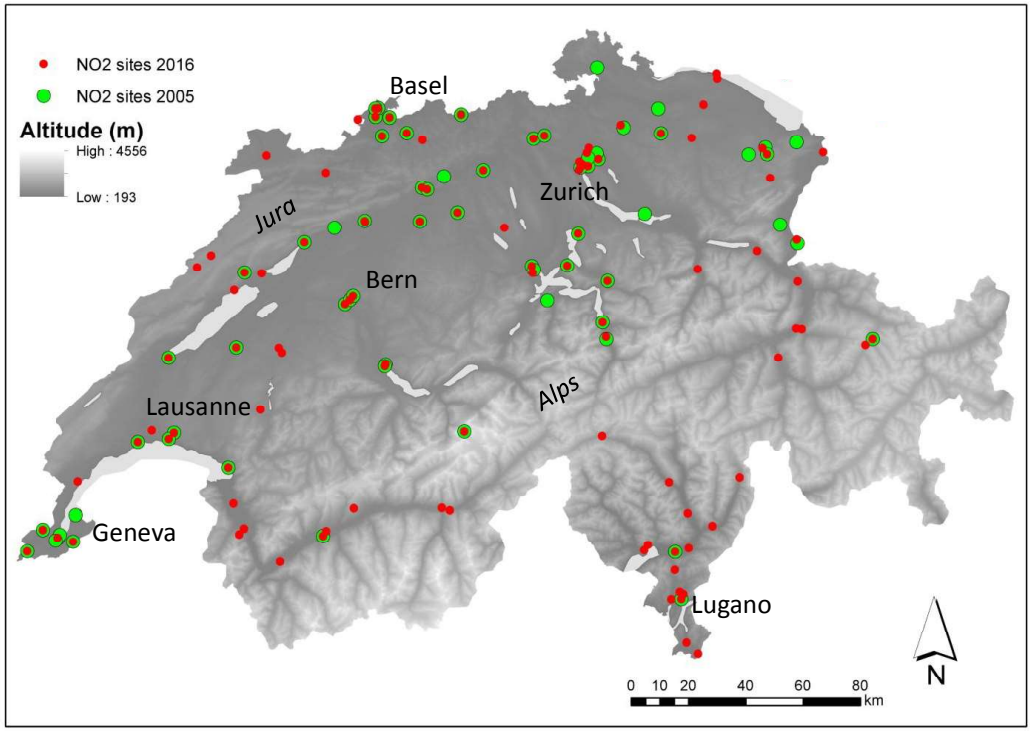


Figure S1. NO_2 monitoring sites locations in 2005 and 2016

Appendix B: Supplementary materials from Chapter 5

Does nighttime aircraft noise trigger mortality? A case-crossover study on 24'886 cardiovascular deaths

Apolline Saucy[1,2], Beat Schäffer[3], Louise Tangermann[1,2], Danielle Vienneau[1,2], Jean-Marc Wunderli[3], Martin Röösli[1,2]

[1] Swiss Tropical and Public Health Institute (Swiss TPH), Basel, Switzerland

[2] University of Basel, Basel, Switzerland

[3] Swiss Federal Laboratories for Materials Science and Technology (Empa), Dübendorf, Switzerland

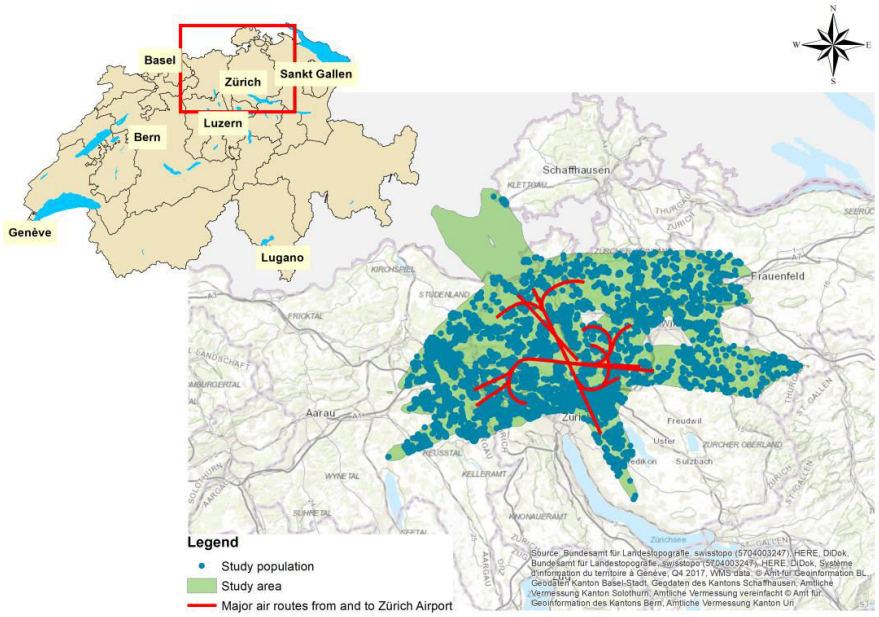


Figure S1: Overview of the selected study population, together with the major air routes from Zürich airport (ZRH). The study population is represented as blue dots, the study area as a green shape and the major departure air routes in red. ZRH is an international airport, subject to a flight restriction during night hours (00:30-05:00 (approaches) and 06:00 (departures) in 2000, and 23:30 to 06:00 since 2010). ZRH counted about 325'000 movements in 2000 and 365'000 in 2015, from which about 3% occured between 23:00 and 07:00.

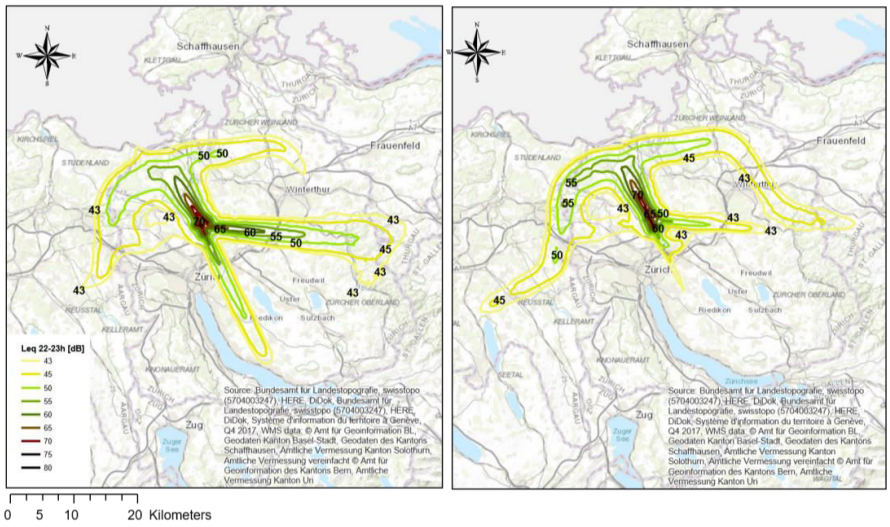


Figure S2: Annual average aircraft noise exposure around Zürich Airport in 2015 for the first night hour on the left (22-23h), and the second night hour on the right (23-24h).

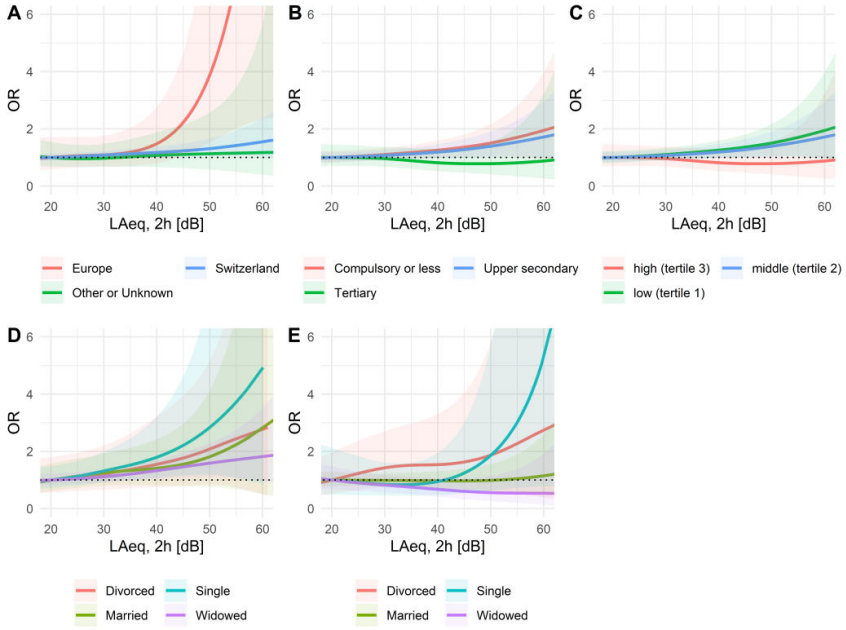


Figure S3: Odds ratio (OR) of nighttime mortality in relation to 2h-L_{Aeq} levels, stratified by (A) nationality, (B) education level, (C) long-term railway and road traffic noise (energetic sum of the noise exposures), (D) civil status for females and (E) males separately.

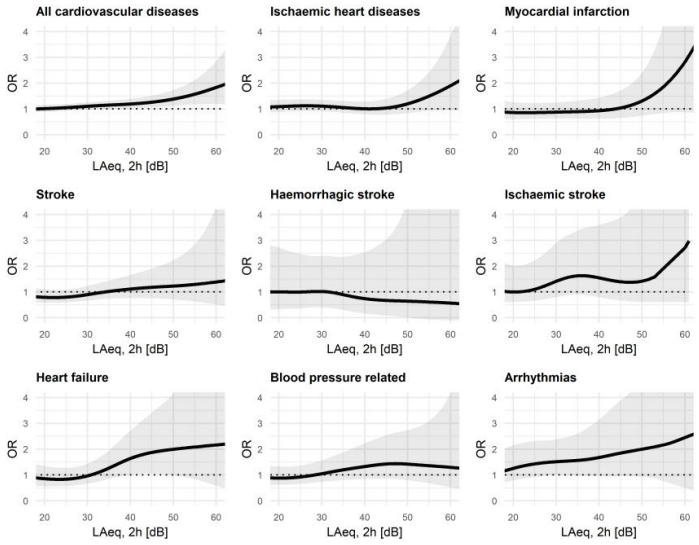


Figure S4: Odds of mortality for increasing 2h-L_{Aeq} levels. Models adjusted for $PM_{2.5}$ (2 days averages) Additionally to NO_2 used for the main analysis. We used modelled daily $PM_{2.5}$ at 100 m × 100 m spatial resolution, available from 2003 onwards for Switzerland. For the earlier years, we calculated individual $PM_{2.5}$ levels using routinely collected data from the nearest 'Immisionsdatenbank Luft (IDB)' (IDB Luft, Bern, Switzerland) combined with the annual mean observed in 2003.

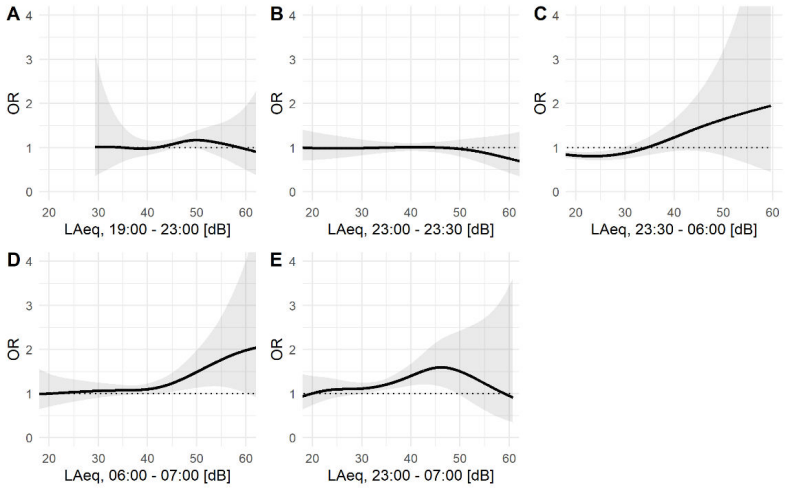


Figure S5: Odds ratio (OR) of daytime mortality from arrhythmias in relation to L_{Aeq} levels for various night-time exposure windows in the night preceding the event: (A) late evening (19:00 to 23:00 h); (B) reduced air traffic (23:00 to 23:30 h); (C) core night (23:30 to 06:00 h); (D) early morning (06:00 to 07:00 h); and (E) overall night (23:00 to 07:00 h).

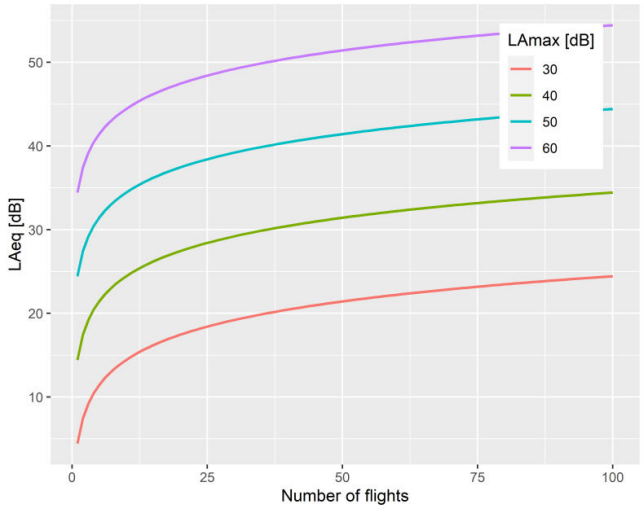


Figure S6: Relation between the number of flights occurring within 1 hour and the average noise level (L_{Aeq}) of each of these flights for different levels of L_{Amax} (30, 40, 50, and 60 dB). We assumed a typical difference between maximum (L_{Amax}) and event (L_{AE}) levels of 10 dB, derived from a large database of flight measurement data. Outdoor 2h-L_{Aeq} levels of 30 dB might seem quite low to be heard indoors and to be associated with potential health effects. However, considering night-time exposure window with only few flights per hour (flight ban in Zürich Airport between 23:30 and 06:00), these low 2h-LAeq might very well represent audible individual flight events. For instance, for a 2h exposure window and considering one flight per hour, a L_{Aeq} of 30dB corresponds to a maximum level of approximately 56dB, which is audible indoors with open or tilted windows. In contrast, lower L_{Aeq} levels below 20dB will hardly be audible and are subject to increased calculation uncertainty. For these reasons, 20dB is taken as a reference level for L_{Aeq} and 40dB for L_{Amax}.

Appendix C: Supplementary materials from Chapter 6

The role of extreme temperature in cause-specific acute cardiovascular mortality in Switzerland: a case-crossover study

Apolline Saucy[1,2], Martina S. Ragettli[1,2], Beat Schäffer[3], Louise Tangermann[1,2], Danielle Vienneau[1,2], Kees de Hoogh[1,2], Jean-Marc Wunderli[3], Martin Röösli[1,2]

[1] Swiss Tropical and Public Health Institute (Swiss TPH), Basel, Switzerland

[2] University of Basel, Basel, Switzerland

[3] Swiss Federal Laboratories for Materials Science and Technology (Empa), Dübendorf, Switzerland

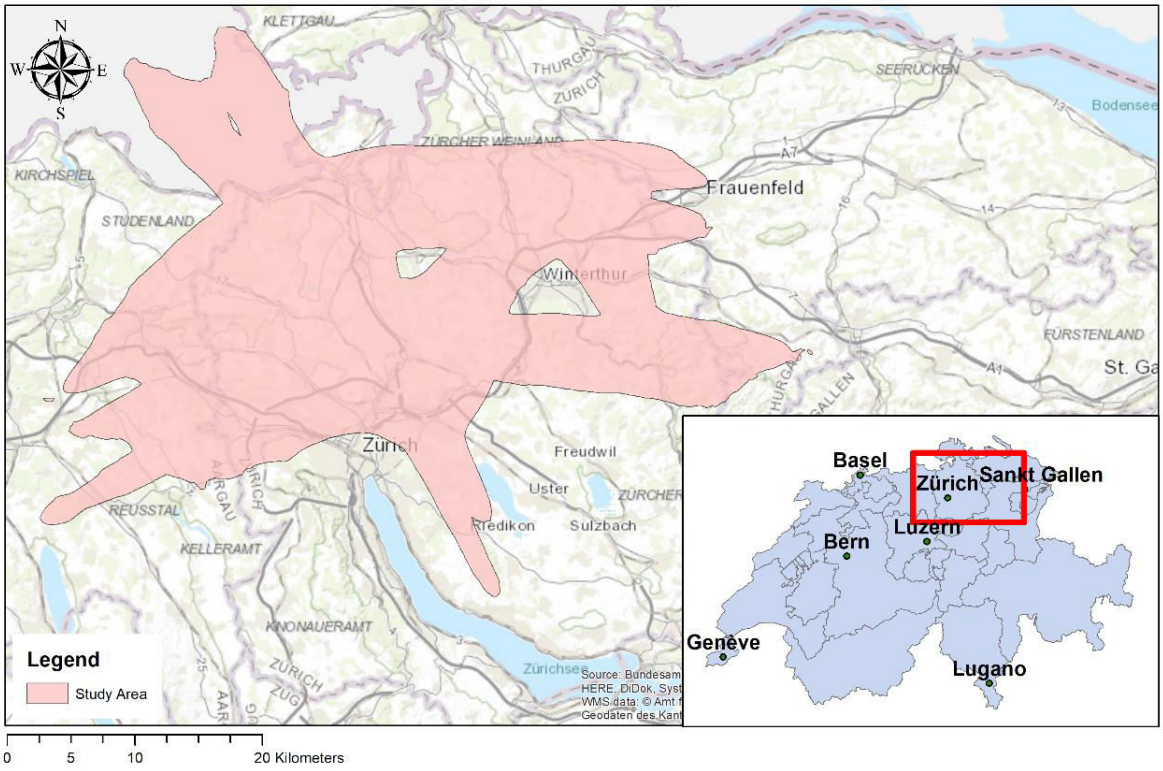
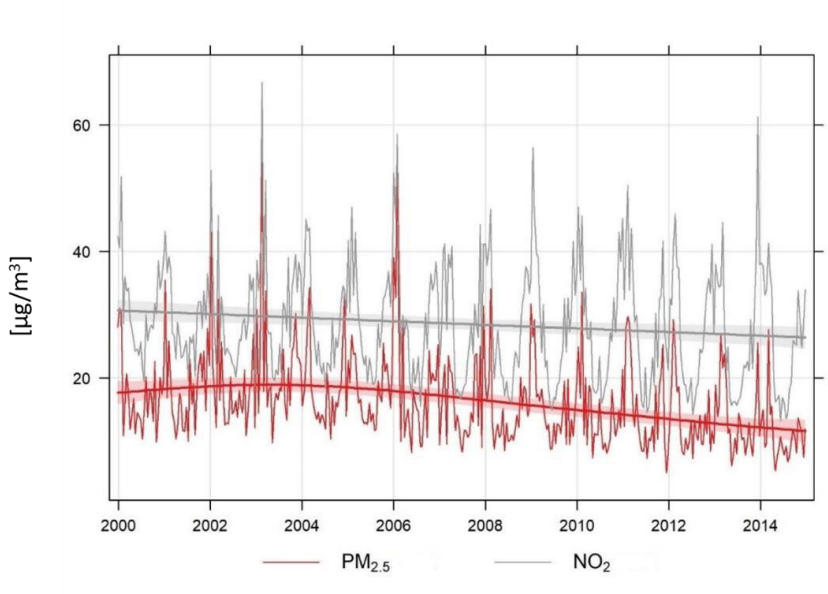


Figure A.1: Overview of the study area (in light red) located near Zurich Airport, Switzerland.



Overview of the time-series data for NO_2 and $PM_{2.5}$ monitored data at Dübendorf located in the centre of the study area for the years 2000 to 2014.

Figure A.2: Calculation of the daily NO_2 and $PM_{2.5}$ at individual home location for the years preceding the available models at 100 × 100 m resolution, following a two-stage modelling strategy.

A first NO_2 and $PM_{2.5}$ daily estimate was calculated using (1), where P is the air pollution estimate and the subscript "i" represents the specific day of interest, "j" each individual home location location, and "D" Dübendorf monitoring station. The subscript "mean" corresponds to the yearly average for the first year of the available model (2005 for NO_2 and 2003 for $PM_{2.5}$). The air pollution estimates modelled in (1) were validated by applying the same imputation approach to impute the data from 2005 to 2015 and 2003 to 2015 for NO_2 and $PM_{2.5}$ respectively and comparing the results with the modelled data available at 100 × 100 m resolution (Pearson correlation coefficient = 0.88 for NO_2 and 0.87 for $PM_{2.5}$).

$$P_{i,j} = P_{j,\,mean} - P_{D,\,mean} + P_{D,\,i} \quad (1)$$

In a second step, the estimate calculated in (1) is refined using a random forest modelling approach calibrated with daily values from Dübendorf monitoring station, Julian day, and x and y coordinates (2). Out of the box cross-validation R^2 from (2) was 96% for NO_2 and 97% for $PM_{2.5}$.

$$P_{rf} = P_{i,j} + P_{D,\,i} + x_j + y_j + Julian\_day_i \quad (2)$$

For $PM_{2.5}$, data which were only measured every 5th day, we used the $PM_{2.5}/PM_{10}$ ratio on available days to impute daily $PM_{2.5}$ missing values.

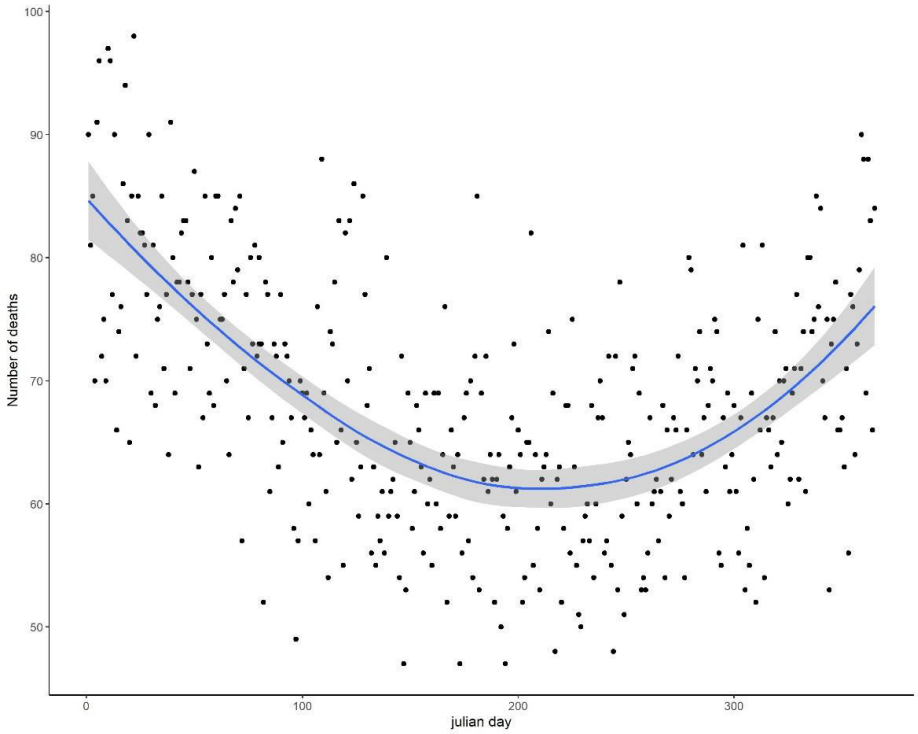


Figure A.3: Evolution of the number of deaths over the year. More cardiovascular deaths were observed during the summer than the winter.

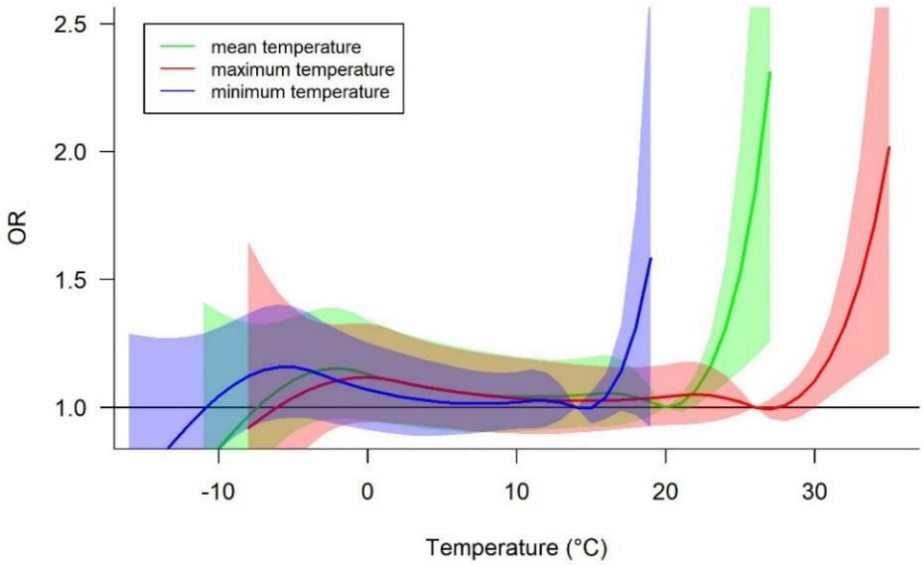


Figure A.4: Cumulative OR of cardiovascular mortality for mean, minimum and maximum temperatures (lags 0-14).

Equation A.1: Conditional logistic regression model where M is the binary variable for mortality, Id is the personal identifier, β_n is the coefficient of the n^{th} variable, AN_{norm} is the normalized night-time aircraft noise level, Hol is the binary variable for public holiday and Fir for firework day. The interaction variable I is in turn NO_2, $PM_{2.5}$, and AN_{norm}.

$$Logit(M|Id) = \beta_0 + \beta_1 \times T_{mean} + \beta_2 \times (T_{mean})^2 + \beta_3 \times I + \beta_4 \times T_{mean} \times I + \beta_5 \times (T_{mean})^2 \times I + \beta_6 \times AN_{norm} + \beta_7 \times PM_{2.5} + \beta_8 \times NO_2 + \beta_9 \times Hol + \beta_9 \times Fir$$

Table A.1: Odds Ratio of cardiovascular mortality for warm temperatures (deviation of Tmean from the 90th (20°C) to the 99th percentile (24°C) of the annual temperature distribution), stratified by gender, education and socio-economic status. Statistically significant results (α=5%) are marked in bold.

	All		***Females***		***Males***	
Age groups						
< 75	5632	1.11 (0.82-1.50)	1762	1.21 (0.70-20.9)	3870	1.06 (0.74-1.53)
75-85	7667	**1.48 (1.15-1.91)**	3692	**1.58 (1.08-2.30)**	3975	1.40 (0.98-1.97)
> 85	12079	**1.28 (1.04-1.59)**	8021	**1.45 (1.13-1.88)**	4058	0.94 (0.64-1.42)
Education						
Compulsory or less	8830	**1.49 (1.17-1.91)**	6660	**1.67 (1.26-2.20)**	2170	0.97 (0.56-1.65)
Upper secondary	12353	**1.25 (1.02-1.55)**	5756	1.21 (0.88-1.64)	6597	1.30 (0.98-1.72)
Tertiary	3150	0.97 (0.65-1.45)	521	1.01 (0.39-2.63)	2629	0.93 (0.59-1.47
Socio-economic status						
Low (1st tertile)	8106	1.20 (0.92-1.55)	4393	1.33 (0.95-1.88)	3713	1.02 (0.69-1.54)
Middle (2nd tertile)	23502	**1.29 (1.11-1.50)**	19789	**1.35 (1.15-1.58)**	19109	**1.28 (1.08-1.51)**
High (3rd tertile)	7666	**1.38 (1.07-1.80)**	3215	1.09 (0.74-1.62)	3880	**1.65 (1.17-2.35)**

Appendix D: Supplementary materials from Chapter 7

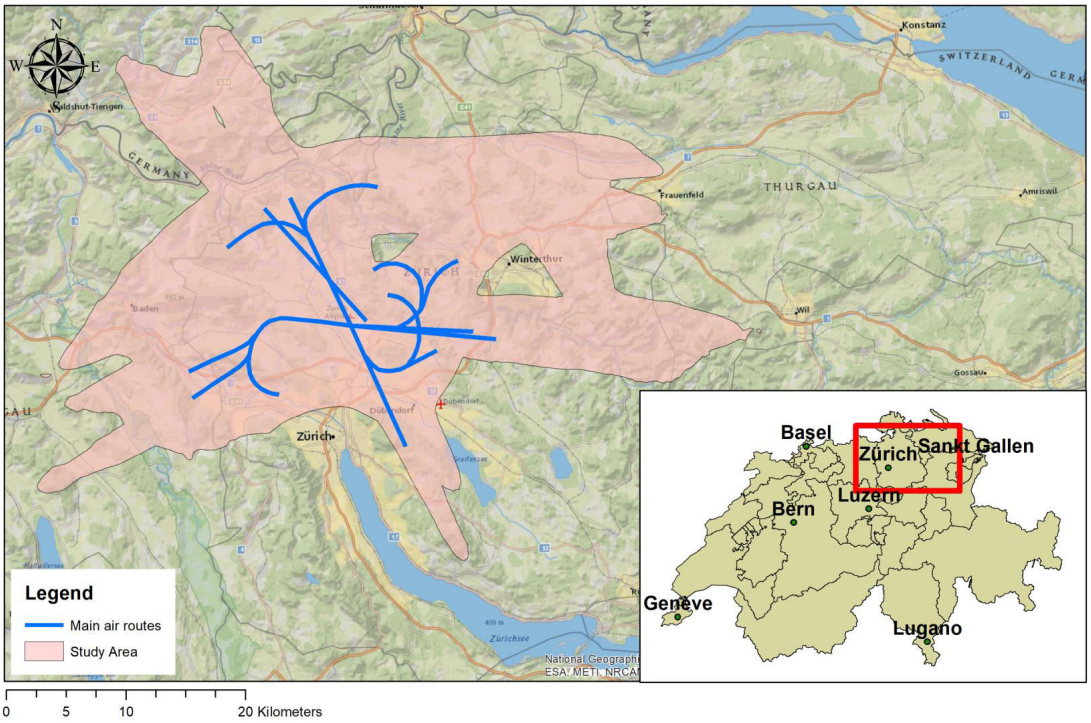
Mutual effects of particulate matter and nitrogen oxide on cause-specific acute cardiovascular mortality: a case-crossover study in Switzerland

Apolline Saucy[1,2], Kees de Hoogh[1,2], Danielle Vienneau[1,2], Louise Tangermann[1,2], Beat Schäffer[3], Jean-Marc Wunderli[3], Martin Röösli[1,2]

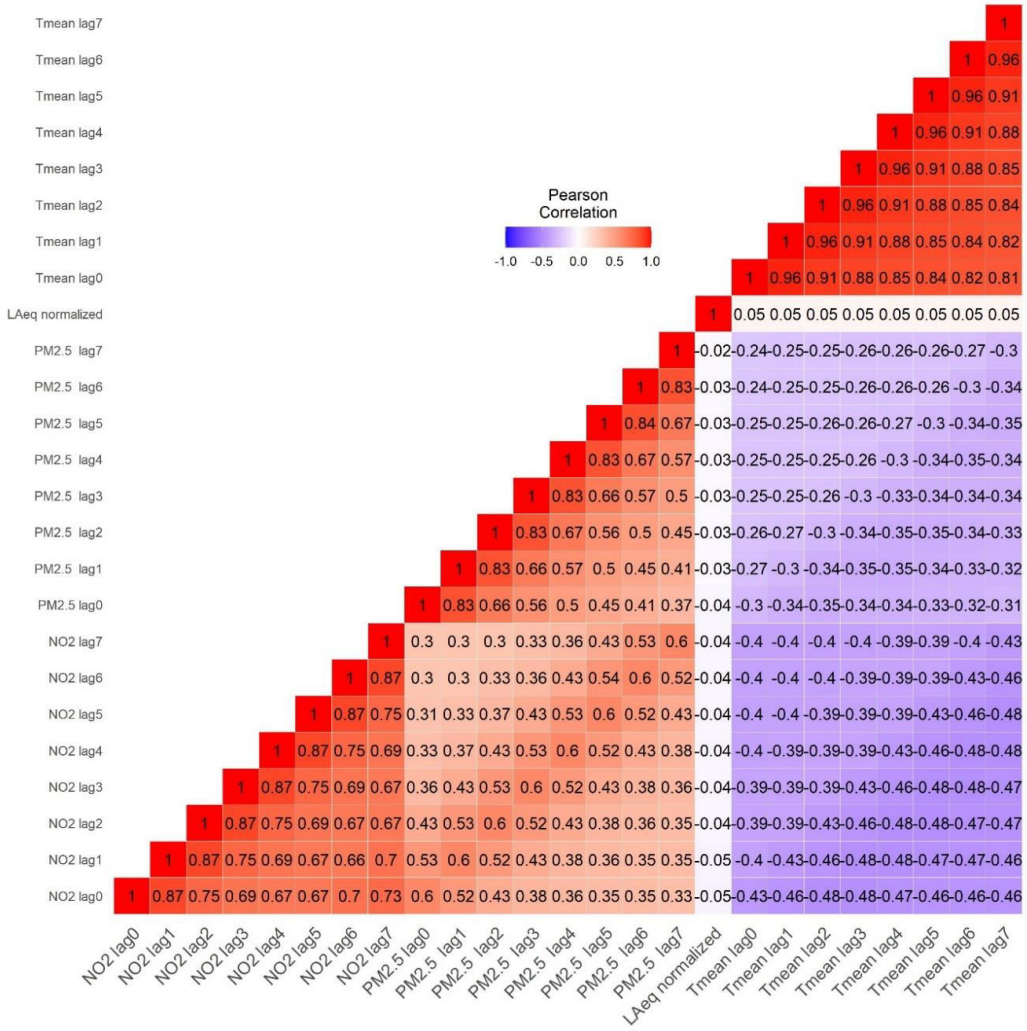
[1] Swiss Tropical and Public Health Institute (Swiss TPH), Basel, Switzerland

[2] University of Basel, Basel, Switzerland

[3] Swiss Federal Laboratories for Materials Science and Technology (Empa), Dübendorf, Switzerland



Supplementary Figure 1: Overview of the study area (light pink shape) located around Zurich airport. The main air routes are displayed as blue lines.



Supplementary Figure 2: Correlation heatmap between and within the different exposure variables (NO_2, $PM_{2.5}$ and T_{mean} lag 0-7, normalized aircraft noise [L_{Aeq}]).

Supplementary Equation 1: Conditional logistic regression model where M is the binary variable for mortality, Id is the personal identifier, β_n is the coefficient of the n^{th} variable, AN_{norm} is the normalized night-time aircraft noise level, Hol is the binary variable for public holiday and Fir for firework day. I is the interaction variable representing individual characteristics and acute night-time aircraft noise (in turn).

$$Logit(M|Id) = \beta_0 + \beta_1 \times T_{mean} + \beta_2 \times (T_{mean})^2 + \beta_3 \times I + \beta_4 \times T_{mean} \times I + \beta_5 \times (T_{mean})^2 \times I + \beta_6 \times AN_{norm} + \beta_7 \times PM_{2.5} + \beta_8 \times NO_2 + \beta_9 \times Hol + \beta_9 \times Fir$$

Extension of the $PM_{2.5}$ nationwide models at 100 m × 100 m resolution for the years 2014–2016.

For this study and possible future studies conducted in Switzerland, we extended the existing daily $PM_{2.5}$ concentrations models to the years 2014 to 2016. Only 2014 and 2015 were needed for the present study, but 2016 was included to match the extent of the previously modelled NO_2 at identical spatiotemporal resolution [1]. We followed a similar 4-stage modelling approach as presented by de Hoogh et al. for the 2003–2013 daily nationwide $PM_{2.5}$ models [2].

As input data, we used PM_{10} and $PM_{2.5}$ routinely monitored data for the years 2014–2016 from the regulatory monitoring network for Switzerland, NABEL [3]. We used the $PM_{2.5}/PM_{10}$ ratio at the 9 co-located sites to impute daily $PM_{2.5}$ in all available 95 PM_{10} monitoring stations. Further input data were MAIAC spectral AOD data derived from MODIS available at 1 × 1 km resolution [4], as well as spatial and temporal predictors including (a) emission data from Meteotest [5], (b) elevation data from the Swiss Federal Office of Topography, (c) land cover from European Corine Landcover, (d) meteorology data from the European Centre for Medium-Range Weather Forecasts [6], and (e) NDVI from the LANDSAT8 satellite. Spatial and temporal predictors were extracted for each 1 × 1 km AOD grid cell to inform stage 1-3 models. Local predictors were extracted at 100 × 100 m resolution within the 1 km × 1 km grid cells to inform the stage 4 models. The four-stage modelling approach is summarized below. More details and modelling equations are available from de Hoogh and colleagues [2].

Stage 1: For each AOD grid cell, we fitted a mixed-effects model to predict the $PM_{2.5}$ concentration from the nearest monitoring station, including fixed effects for AOD, boundary layer, wind speed, wind direction, temperature, precipitation, NDVI and spatial predictors at 1 × 1 km, and random slope for Julian day and climatic region. Each year's $PM_{2.5}$ was estimated in a separate model.

Stage 2: $PM_{2.5}$ was estimated in all 1 × 1 km grid cells with available AOD data and missing monitored or imputed $PM_{2.5}$ monitoring stations using the stage 1 model.

Stage 3: $PM_{2.5}$ was estimated in all grid cells with missing AOD data using spatial smoothing with a thin plate spline for each cell and day of the year.

Stage 4: $PM_{2.5}$ was estimated at the local 100 × 100 m level by fitting a support vector machine algorithm to the residuals from stage 1 model at locations with monitored and imputed $PM_{2.5}$ data. The modelled residuals were finally added to the stage 3 models, resulting in daily local $PM_{2.5}$ modelled data at 100 × 100 m resolution.

Summary statistics of the global model performance at 1 km × 1 km grid cells level:

Year	R2	Intercept	Slope	RMSE	CV R^2	CV RMSE	Spatial R^2	CV spatial R^2	Temporal R^2	CV temporal R^2
2014	0.826	-1.274	0.980	3.344	0.76	3.96	0.568	0.67	0.867	0.80
2015	0.751	-3.535	1.020	3.848	0.69	4.35	0.634	0.73	0.796	0.71
2016	0.717	-4.193	0.999	4.075	0.67	4.54	0.571	0.72	0.763	0.67

Summary statistics of the local model performance (stage 4) at 100 m × 100 m level:

Year	Total R^2	Slope	RMSE	Spatial R^2	Spatial RMSE	Temporal R2	Temporal RMSE
2014	0.888	1.032	2.767	0.960	0.675	0.879	2.697
2015	0.865	1.037	2.845	0.981	0.465	0.842	2.802
2016	0.840	1.068	3.097	0.977	0.468	0.819	3.066

Supplementary Table 1: Crude and mutually adjusted Odds ratios (95% CI) for different exposures from the multi-pollutant models. All the models are adjusted for precipitation and mean temperature (2-days average). The main models are adjusted for acute night-time aircraft noise, NO_2, $PM_{2.5}$, firework days and national holidays. Adjustment for aircraft noise was done using a combination of normalized L_{Aeq}(2h) for night-time deaths and normalized L_{Aeq} (23:00-07:00) for daytime deaths.

Variables	Main model [a]	Model1 [b]	Model2 [c]	Model3 [d]	Model4 [e]
L_{Aeq}(2h)*	1.06 (1.00-1.13)	-	1.06 (1.00-1.12)	1.06 (1.00-1.13)	1.06 (1.00-1.12)
NO_2	1.04 (1.00-1.08)	1.04 (1.00-1.08)	-	1.03 (1.01-1.06)	1.04 (1.00-1.08)
$PM_{2.5}$	0.98 (0.95-1.02)	0.98 (0.95-1.02)	1.01 (0.99-1.03)	-	0.99 (0.96-1.02)
Firework days	1.29 (1.08-1.54)	1.29 (1.08-1.54)	1.28 (1.07-1.53)	1.29 (1.08-1.54)	-

* Model based on night-time deaths only (time of death between 23:00 and 07:00)

[a] Main model: Fully adjusted multi-pollutant model. AIC = 73429.90

[b] Model1 is adjusted for all covariates except from aircraft noise. AIC = 73430.15

[c] Model2 is adjusted for all covariates except from NO2. AIC= 73432.54

[d] Model3 is adjusted for all covariates except from PM2.5. AIC= 73428.69

[e] Model4 is adjusted for all covariates except from firework days and national holidays. AIC = 13434.35

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1. de Hoogh, K., et al., *Predicting Fine-Scale Daily NO2 for 2005-2016 Incorporating OMI Satellite Data Across Switzerland.* Environ Sci Technol, 2019.
2. de Hoogh, K., et al., *Modelling daily PM2.5 concentrations at high spatio-temporal resolution across Switzerland.* Environmental Pollution, 2017.
3. *NABEL National Air Pollution Monitoring Network*. 2001, Swiss Agency for the Environment, Forests and Landscape (SAEFL): Bern, Switzerland.
4. Lyapustin, A., et al., *Multiangle implementation of atmospheric correction (MAIAC): 2. Aerosol algorithm.* Journal of Geophysical Research: Atmospheres, 2011. **116**(D3).
5. FOEN. *PM10 and PM2.5 Ambient Concentrations in Switzerland, Modelling Results for 2005, 2010, 2020.* 2013; Available from: https://www.bafu.admin.ch/bafu/en/home/topics/air/publications-studies/publications/pm10-and-pm2-5-ambient-concentrations-in-switzerland.html.
6. Dee, D.P., et al., *The ERA-Interim reanalysis: Configuration and performance of the data assimilation system.* Quarterly Journal of the royal meteorological society, 2011. **137**(656): p. 553-597.

Appendix F: Distribution of long-term transportation and short-term aircraft noise

	Total cohort	Total daytime deaths	>50 dB road traffic noise (Lnight)	>50 dB railway noise (Lnight)	>50 dB aircraft noise (Lnight)	>50 dB acute aircraft noise (daytime deaths, LAeq, 23:00-07:00)	>95th percentile road traffic noise (59.1 dB Lnight)	>95th percentile railway noise (50 dB Lnight)	>95th percentile aircraft noise (48.7 dB Lnight)	>95th percentile acute aircraft noise (daytime deaths, 47.6 dB Laeq 23:00-07:00)
	N = 24886	N = 1724	N = 7810	N = 1235	N = 968	N = 581	N = 1211	N = 1235	N = 1222	N = 863
Total	100.0%	100.0%	31.4%	5.0%	3.9%	3.4%	4.9%	5.0%	4.9%	5.0%
Gender										
Female	53.3%	52.8%	31.3%	5.1%	4.1%	3.2%	4.8%	5.1%	5.1%	4.8%
Male	46.7%	47.2%	31.5%	4.8%	3.7%	3.5%	4.9%	4.8%	4.7%	5.2%
Age groups										
<= 75	22.6%	23.2%	31.5%	4.6%	3.9%	3.3%	4.7%	4.6%	5.1%	4.9%
75-85	43.9%	43.1%	31.3%	5.0%	4.0%	3.1%	4.8%	5.0%	5.0%	4.9%
>85	33.4%	33.7%	31.4%	5.2%	3.7%	3.7%	5.1%	5.2%	4.7%	5.2%
*Socio-economic position**										
1	10.1%	9.9%	30.4%	4.8%	3.8%	5.5%	5.2%	4.8%	4.9%	8.4%
2	14.8%	14.9%	32.0%	4.6%	3.5%	6.4%	5.5%	4.6%	4.3%	8.7%
3	18.0%	18.2%	32.0%	5.0%	3.6%	3.6%	4.7%	5.0%	4.7%	5.4%
4	25.2%	25.3%	31.0%	5.2%	4.2%	2.7%	4.5%	5.2%	5.3%	4.0%
5	26.4%	26.4%	31.1%	4.9%	4.0%	1.4%	4.9%	4.9%	5.1%	2.6%
Unknown	5.6%	5.3%	32.9%	5.6%	4.1%	2.7%	4.7%	5.6%	5.1%	3.8%
Education										
Compulsory or less	35.5%	35.2%	31.1%	4.9%	4.0%	3.2%	5.1%	4.9%	5.1%	4.8%
Upper secondary level	49.6%	49.9%	31.7%	5.0%	3.9%	3.6%	4.7%	5.0%	4.9%	5.3%
Tertiary level	12.7%	12.8%	31.0%	5.2%	3.6%	3.0%	5.0%	5.2%	4.6%	4.2%
Unknown	2.2%	2.2%	30.6%	3.8%	3.1%	3.2%	4.7%	3.8%	3.6%	5.9%
Urbanisation										
urban	36.6%	36.4%	31.2%	5.3%	4.2%	4.2%	5.0%	5.3%	5.1%	6.1%
peri-urban	57.7%	57.8%	31.3%	4.7%	3.8%	3.2%	4.7%	4.7%	4.8%	4.8%
rural	5.8%	5.8%	34.0%	4.8%	2.7%	0.0%	5.9%	4.8%	4.2%	0.3%
Building period										
before 1970	28.5%	28.1%	31.6%	5.2%	3.7%	1.7%	4.7%	5.2%	4.5%	4.1%
1970-1990	9.5%	10.0%	31.4%	5.3%	4.3%	5.1%	5.2%	5.3%	5.5%	6.6%
after 1990	60.1%	60.0%	31.4%	4.8%	4.0%	3.8%	4.9%	4.8%	5.0%	5.1%
Unknown	1.9%	2.0%	27.4%	3.6%	2.5%	4.4%	5.5%	3.6%	3.8%	6.2%
Civil status										
Married	37.3%	37.9%	31.4%	4.7%	3.7%	3.4%	4.9%	4.7%	4.8%	4.9%
Non married	62.7%	62.1%	31.3%	5.1%	4.0%	3.3%	4.8%	5.1%	5.0%	5.1%

* Long-term exposure from combined and individual sources (road traffic, railway and aircraft) as calculated within the SiRENE project
(Karipidis I, Vienneau D, Habermacher M, Ko¨ pfli M, Brink M, Probst-Hensch N, Roöösli M, Wunderli J-M.
Reconstruction of historical noise exposure data for environmental epidemiology in Switzerland within the SiRENE project. Noise Mapping 2014;1.
** Acute exposure to aircraft noise as calculated in this thesis (Chapter 3), overall night (23:00 to 07:00), for deaths occuring during the day
*** Swiss neighbourhood index of socioeconomic position. Quintiles.

Appendix G: Noise and cardiovascular risk: nighttime aircraft noise acutely triggers cardiovascular death

Thomas Münzel[1,2*], Sebastian Steven[1], Omar Hahad[1,2], Andreas Daiber[1,2]

[1] Department of Cardiology, Cardiology I, University Medical Center Mainz, Mainz, Germany
[2] German Center for Cardiovascular Research (DZHK), Partner Site Rhine-Main, Mainz, Germany

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doi:10.1093/eurheartj/ehaa984

EDITORIAL

Noise and cardiovascular risk: nighttime aircraft noise acutely triggers cardiovascular death

Thomas Münzel[1,2]*, Sebastian Steven [1], Omar Hahad [1,2], and Andreas Daiber [1,2]

[1]Department of Cardiology, Cardiology I, University Medical Center Mainz, Mainz, Germany; and [2]German Center for Cardiovascular Research (DZHK), Partner Site Rhine-Main, Mainz, Germany

This editorial refers to 'Does night-time aircraft noise trigger mortality? A case-crossover study on 24 886 cardiovascular deaths', by A. Saucy *et al.*, doi: 10.1093/eurheartj/ehaa957.

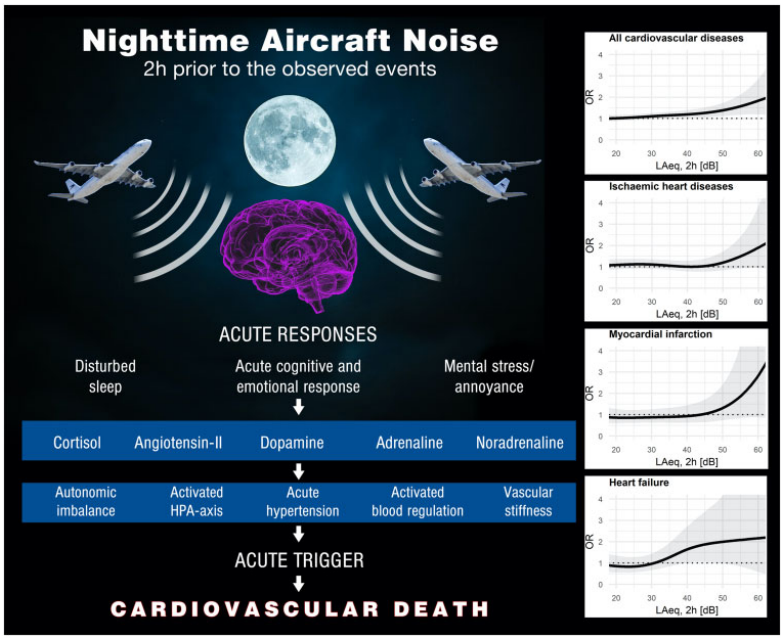

Figure 1 Effects of acute nighttime aircraft noise exposure that lead to cardiovascular death. Inserts (right panel) show substantial odds ratios of nighttime mortality in relation to 2 h-L_{Aeq} levels (energy-equivalent average A-weighted sound pressure level expressed in decibels) as adapted from Saucy *et al.*,[16] with permission.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author. University Medical Center Mainz, Department of Cardiology, Cardiology I, Geb. 605, Langenbeckstr. 1, D-55131 Mainz, Germany. Tel: +49 6131 17 7250, Fax: +49 6131 17 6615, Email: tmuenzel@uni-mainz.de

Environmental transportation noise as a cardiovascular risk factor

Air pollution is an established risk factor for cardiovascular disease (CVD).[1] Much less attention has been devoted so far to environmental noise, which co-exists with air pollution mainly in urban areas.[2] The World Health Organization (WHO) estimates that in Western Europe alone noise exposure causes up to 1.6 million disability-adjusted life years (DALYs) per year. Also the 'cardiovascular burden' of noise is substantial; for the European Union, transportation noise is estimated to result in 900 000 cases of hypertension, 43 000 hospital admissions, and >10 000 premature deaths per year related to coronary heart disease and stroke.[3] Although a large proportion of the population is exposed to transportation noise levels exceeding the recommended guideline levels, traffic noise is not mentioned or only insufficiently addressed as a risk factor in either the Global Burden of Disease (GBD) Study,[4] 'Health at a Glance: Europe 2018', cardiovascular prevention guidelines by the European Society of Cardiology (ESC),[5] or by the American Heart Association/American College of Cardiology (AHA/ACC).[6]

So far, most epidemiological studies have focused on cardiovascular side effects of long-term exposure to transportation noise (for reviews, see Basner *et al.*[7] and Munzel *et al.*[8]). Importantly, translational studies in humans and animals primarily focused on health side effects of nighttime noise with respect to the cardiovascular system.[9] In humans only one night of aircraft noise triggered endothelial dysfunction, increased stress hormone levels, and deteriorated sleep quality.[10] These effects were even more pronounced in patients with already established CVD.[11] The acute administration of the antioxidant vitamin C improved endothelial dysfunction, suggesting an involvement of reactive oxygen species in the pathophysiology of noise-induced vascular dysfunction.[10] Recent animal studies indicated that aircraft noise applied during the sleeping phase of mice, but not during the awake phase, raises blood pressure, dysregulates genes related to the circadian clock and stress hormone levels, causes endothelial dysfunction, and increases cerebral and vascular oxidative stress.[12] These observations may indicate that the disturbance of sleep (e.g. sleep deprivation or fragmentation) may account at least in part for noise-induced cardiovascular damage.

Acute exposure to nocturnal aircraft noise and cardiovascular death

Whereas the acute effects of noise exposure on neuronal stress responses (e.g. activation of the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system) are well established,[13] the acute effects of noise on cardiovascular events and death have not been studied in detail. Epidemiological and translational studies of humans with and without coronary artery disease revealed that nighttime exposure to different transportation noise patterns for only one night adversely affected blood pressure, diastolic heart function, sympathovagal balance, and the plasma proteome.[10,11,14,15]

With their study, in this issue of the *European Heart Journal*, Saucy *et al.* sought to determine the effects of acute exposure to nighttime aircraft noise on cardiovascular death.[16] On the basis of a case-crossover study design, the authors analysed 24 886 cases of death from CVD from the Swiss National Cohort around Zürich Airport between 2000 and 2015. The authors established that for nighttime deaths, aircraft noise exposure levels 2 h preceding death were significantly associated with mortality for all causes of CVD (*Figure 1*). Most consistent associations were observed for ischaemic heart disease, myocardial infarction, heart failure, and arrhythmia. The associations were more pronounced for females and for people living in areas with low road and railway background noise and in buildings constructed before 1970. The authors also calculated a population-attributable fraction of 3% in their study populaion and finally concluded that nighttime noise may trigger acute cardiovascular mortality.

Strengths and limitations of the study

There are several novel and innovative aspects and strengths of this study. To our knowledge, it is the first study worldwide that has addressed acute effects of noise on cardiovascular mortality indicating for the first time that aircraft noise is a trigger for fatal acute coronary events. The case-crossover design is innovative to analyse acute health effects and has not been used for noise research (but is well established for air pollution research). A particular strength of the study design is that health risks are estimated based on the exposure difference between case and control events for the same person and the same location. This implies that several potential biases, which are of concern in cohort studies, are hardly relevant (e.g. confounding from individual lifestyle factors, selection bias, etc.). In this study, a high precision aircraft noise modelling was used. The researchers used radar records from each flight between 2000 and 2015. Thus, the study accounts for single, specific flight events, yielding individual aircraft noise exposure estimates with high spatial and temporal accuracy for each death and control event. The large sample size and the absence of selection bias as every cardiovascular death within the study area was included is remarkable. The study allowed calculation of the attributable fraction: ~3% of cardiovascular nighttime deaths are attributable to aircraft noise. Furthermore, the study compared the effects for different time windows of exposure, which is scarcely possible in cohort studies due to high correlation. It clearly supports the substantial relevance of nighttime noise as already suggested by epidemiological and animal research.[9]

However, some limitations have to be taken into account. Due to the nighttime flight restriction in place at Zürich Airport, the noise levels were rather low and thus the findings should be reproduced at airports with higher nighttime noise exposure levels. Also, the authors did not consider daytime noise exposure for the analysis of daytime deaths, because they expected substantial exposure misclassification when people are not at home during the day.

What are the societal and political consequences?

Taken together, the present study describes for the first time acute effects of noise on cardiovascular mortality indicating that aircraft noise is a trigger for fatal acute coronary events. If these findings are confirmed by further studies at airports with higher nighttime noise exposure, a complete ban on nighttime flights must be the consequence. There is now substantial evidence that (aircraft) noise is a cardiovascular risk factor that cannot be modified by patients or doctors, but rather by politicians and the cardiovascular societies such as the ESC and AHA/ACC reinforcing, for example, the new noise limits published in the WHO guidelines concerning road, aircraft, and railway noise.[2]

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