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ENVIRONMENTAL EXPOSURES AND CARDIAC ARRHYTHMIAS

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Environmental Exposures and Cardiac Arrhythmias

Thesis for Doctoral Degree (Ph.D.)

By

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To Emma and Frida

Popular science summary of the thesis

Human health is affected by the environment. What we eat, breath and are exposed to will have consequences for increased or decreased risk of disease. In this thesis I have focused on two exposures, air temperature and air pollution, that affect people all over the world with a substantial impact on health. While there is mounting evidence of negative health effects of both air temperature and air pollution there remains a knowledge gap on potential effects on heart rhythm disturbances (arrhythmias).

We studied two different arrhythmias. Firstly, the most severe arrhythmia, cardiac arrest, is an electrical disturbance in heart that causes the heart to stop, resulting in the patient falling unconscious and facing imminent death if not treated. Currently only about 11 % of people suffering a cardiac arrest at home or in public survive, even with medical treatment. Every year approximately 300,000 people die of cardiac arrest in Europe. The second arrhythmia we studied is the most common arrhythmia among adults, atrial fibrillation. This is an electric disturbance in the atria of the heart causing irregular and often rapid heartbeat. The disease can be either permanent or transient, with a wide range of clinical presentations. Some patients have severe symptoms and reduced quality of life while others don't have any symptoms at all. Atrial fibrillation is known to increase the risk of stroke and increased risk of premature death.

We conducted four studies investigating air temperature or air pollution exposure and the risk of cardiac arrest or atrial fibrillation. All studies investigated short-term effects, meaning hourly or daily changes in levels of exposures and how these are related to the risk of arrhythmia episodes. Three of the studies (Study I, III and IV) were conducted in Stockholm using fixed temperature or air pollution monitors strategically located to represent urban background levels. In this way everyone in Stockholm was assigned the same exposure for a given hour or day regardless of where they lived. In contrast, Study II was conducted on a national level in Sweden and used an advanced air pollution exposure model based on a validated machine learning algorithm that uses information from several different sources (for example satellite data, mathematical models, and information on roads, traffic and industries) to estimate air pollution levels in 1x1 km grids. Each case of cardiac arrest was, in this study, assigned an air pollution exposure based on the grid cell it occurred in.

Study I. In this study we investigated the association between air temperature and risk of cardiac arrest. Temperature data was collected from a meteorological station. For cardiac arrest, we used a registry with data collected by first-responders (ambulance personnel, firefighters, and police) to a cardiac arrest and who performed cardiopulmonary resuscitation (CPR). The registry has information on when and where the cardiac arrest occurred. We analyzed how preceding levels of outdoor temperature increased the risk of suffering a cardiac arrest. In summary, we observed the lowest risk

of cardiac arrest when the temperature was around 12 degrees Celsius with clear increased risks for daily temperatures going below 12 degrees and suggested increased risks for daily temperatures rising above 12 degrees.

Study II. In the second study we investigated the association between air pollution and cardiac arrest. We used the same registry as for Study I and combined that with estimated air pollution levels from the national air pollution model based on the machine learning methodology. Higher levels of air pollution particles were associated with an increased risk of cardiac arrest four days following exposure. The risk was observed for both men and woman, younger and older and for people living in cities as well as in the countryside.

Study III. In the third study we investigated the association between air pollution and risk of suffering an atrial fibrillation episode. We used data from participants that underwent atrial fibrillation screening. Participants were examined with an electrocardiogram (ECG) at home 2-4 times per day for 14 days to capture both symptomatic and asymptomatic occurrences of atrial fibrillation. Hourly air pollution levels were collected from fixed monitoring stations and changes in levels were compared to occurrence of atrial fibrillation in each individual. Higher air pollution levels increased the risk of atrial fibrillation within 12-24 hours of exposure. The risk was especially high for participants with diabetes and overweight.

Study IV. In Study IV we recruited participants with pacemakers at their regular follow ups at the arrhythmia clinic. A pacemaker can recognize, and store episodes of atrial fibrillation, information that is possible to extract at each follow up. We used this to collect episodes of atrial fibrillation and then compared air pollution levels before the atrial fibrillation episodes with similar timepoints when the participants had normal heart rhythm. We found that higher levels of air pollution particles increased the risk of atrial fibrillation onset.

In summary exposure to air temperature and air pollution increased the risk of arrhythmias. We observed that cold temperatures were related to an increased risk of having a cardiac arrest, and air pollution exposure was related to increased risk of having a cardiac arrest and of experiencing episodes of atrial fibrillation.

Abstract

Cardiac arrhythmias lead to substantial mortality and morbidity world-wide. The most severe form of cardiac arrhythmia, cardiac arrest, is one of the leading causes of death in Europe and North America. Further, the prevalence of atrial fibrillation, the most common arrhythmias among adults, is expected to increase substantially during the coming decades with increased mortality and morbidity as a consequence. At present atrial fibrillation affects more than 30 million people world-wide. Ambient environmental exposures, i.e. temperature and air pollution, have a well-established association to cardiovascular disease with significant health impact. The association to cardiac arrhythmias is less well understood.

The aim of this thesis was to investigate the associations between short-term exposure to ambient temperature, and air pollution with out-of-hospital cardiac arrest, hereafter referred to as cardiac arrest, and atrial fibrillation.

In Study I we investigated the association between ambient temperature and cardiac arrest. The study included 5,961 cases of cardiac arrest in Stockholm. We observed a V-shaped relationship between preceding mean 24-hour and 1-hour ambient temperature and the occurrence of cardiac arrest with statistically significant associations for temperatures below the optimum temperature.

In Study II we investigated the association between short-term air pollution exposures and cardiac arrest. We estimated daily air pollution levels in 1x1 km grids using a satellite-based machine learning model. Among 29,604 cases of cardiac arrests from all of Sweden we observed a higher risk associated with short-term particulate matter <2.5 μm ($PM_{2.5}$) and particulate matter <10 μm (PM_{10}) exposure.

In Study III we investigated short-term air pollution exposure and risk of atrial fibrillation episodes in 75-year-olds living in Stockholm, Sweden that underwent atrial fibrillation screening. We estimated air pollution exposure by use of single fixed monitors representing urban background levels. Among 218 participants with 469 episodes of atrial fibrillation we observed increased risks associated with PM_{10} exposure. The associations were more pronounced for participants with overweight and diabetes.

In Study IV we investigated the association between air pollution and atrial fibrillation in patients with intracardiac devices, i.e. pacemakers, able to store atrial fibrillation episodes. Air pollution exposure was assessed in a similar way as in Study III. 91 participants contributed data to the final analysis of 584 episodes of atrial fibrillation. We observed increased risk of atrial fibrillation episodes with short-term exposure to $PM_{2.5}$.

In conclusion, our findings indicate an increased risk of cardiac arrhythmias with exposure to ambient temperature and air pollution. We observed associations for air pollution exposure even at very low levels, below current regulatory guidelines.

List of scientific papers

I. **Dahlquist M,** Raza A, Bero-Bedada G, Hollenberg J, Lind T, Orsini N, Sjögren B, Svensson L, Ljungman P. Short-term departures from an optimum ambient temperature are associated with increased risk of out-of-hospital cardiac arrest. *Int J Hyg Environ Health. 2016 Jul;219(4-5):389-97.*

II. **Dahlquist M,** Frykman V, Hollenberg J, Jonsson M, Stafoggia M, Wellenius G, Ljungman PLS. Short-term ambient air pollution exposure and risk of out-of-hospital cardiac arrest in Sweden: A nation-wide study. *Submitted.*

III. **Dahlquist M,** Frykman V, Kemp-Gudmunsdottir, Svennberg E, Wellenius GA, Ljungman PLS. Short-term associations between ambient air pollution and acute atrial fibrillation episodes. *Environ Int. 2020 Aug;141:105765*

IV. **Dahlquist M,** Frykman V, Stafoggia M, Qvarnstrom E, Wellenius GA, Ljungman PLS. Short-term ambient air pollution exposure and risk of atrial fibrillation in patients with intracardiac devices. *Environ Epidemiol. 2022 Jul 22;6(4):e215*

Contents

List of abbreviations

AOD	Aerosol optical depth
BMI	Body mass index
CO	Carbon monoxide
CI	Confidence interval
CRT	Cardiac resynchronization therapy
ECG	Electrocardiogram
EGM	Electrogram
EMS	Emergency medical services
EU	European Union
GEE	Generalized estimating equations
ICD	Implantable cardioverter defibrillator
IPCC	Intergovernmental Panel on Climate Change
IQR	Interquartile range
LDL	low-density lipoprotein
NO_2	Nitrogen dioxide
NO_x	Nitrogen oxides
OR	Odds Ratio
O_2	Oxygen
O_3	Ozone
PM	Particulate matter
$PM_{0.1}$	Particulate matter with a diameter < 0.1 µm, ultrafine particles
$PM_{2.5}$	Particulate matter with a diameter < 2.5 µm, fine particles
PM_{10}	Particulate matter with a diameter < 10 µm
$PM_{10-2.5}$	Coarse particulates with a diameter 2.5–10 µm, coarse particles
PVC	Premature ventricular contractions
PEA	Pulseless electrical activity
SO_x	Sulphur oxides
SRCR	Swedish Registry of Cardiopulmonary Resuscitation
TIA	Transient ischemic attack
VF	Ventricular fibrillation
VT	Ventricular tachycardia
VOC	Volatile organic compounds
WHO	World Health Organization

Introduction

Cardiac arrhythmias incur significant impact on health globally (1) and in Sweden (2). The most severe form of cardiac arrhythmia, cardiac arrest, is one of the leading causes of death in Europe and North America (3). The prevalence of atrial fibrillation, the most common arrhythmias among adults, is expected to increase substantially during the coming decades (4) with increased mortality and morbidity as a consequence. The etiology of cardiac arrhythmic disease is multi-factorial and well-established risk-factors include unmodifiable factors such as age, family history, and sex as well as modifiable risk factors such as smoking, obesity and blood lipid levels (5, 6). During the last couple of decades an increasing body of literature has shown several environmental exposures to be risk-factors of cardiovascular disease (7). Even though the relative risk increase for environmental exposure is often small, the exposure is frequently widespread including the majority of the population with little to no individual ability of affecting the personal exposure. This results in a great burden on health from air pollution and ambient temperature exposures. In the latest global burden of disease ambient air pollution is attributed to 6.7 million deaths per year with the majority being cardiovascular deaths (8). Estimates for temperature exposure have recently been added to the global burden of disease project and are estimated to contribute to an additional 1.9 million deaths annually (8). In Sweden an estimated 7,800 annual deaths are related to air pollution (9).

A potential association to arrhythmic diseases such as cardiac arrest and atrial fibrillation is less well understood and insufficiently studied. There is a limited number of studies investigating temperature and cardiac arrest and most of previous studies investigating air pollution and arrhythmias have been conducted in areas with air pollution levels above the new World Health Organization (WHO) air quality guidelines and the current levels in Sweden. This highlights the need for investigating ambient temperature and air pollution exposure relation to cardiac arrhythmias, especially in areas with relatively low air pollution levels.

1 Literature review

1.1 Ambient Air Pollution

Air pollution is a complex mix of gases and particles in the atmosphere with adverse effects on human health, living organisms and the climate. The mix and concentration of the different pollutants varies with different emission sources, geography, temperature, relative humidity, wind and other atmospheric properties. Gaseous and particulate matter air pollution have different chemical properties and qualities and research has provided scientific evidence of negative health effects for multiple pollutants. This evidence has led to regulatory measures to limit population exposure of criteria pollutants.

1.1.1 Gases

Carbon monoxide (CO), Nitrogen oxides (NO_x) and Sulphur oxides (SO_x) are all primary pollutants emitted during combustion of fuel or organic material. Emissions originate from both anthropogenic sources such as fossil fuel power stations, manufacturing facilities, waste burning, motor vehicle exhaust and for NO_x fertilized farmlands, as well as natural sources such as wildfires and volcanic eruptions. The main secondary pollutant is ground level Ozone (O_3) that is created through a reaction of NO_x or hydrocarbons with Oxygen (O_2) during the presence of ultra-violet light. O_3 is thus not emitted directly but sources emitting NO_x, CO and volatile organic compounds (VOC) result in higher background levels of O_3. NO_2 is partly emitted as a primary pollutant from combustion but the main source is secondary creation from NO_x reacting with O_3 and thus creating NO_2 and O_2. This can result in contra intuitive lower levels of O_3 close to emission sources.

With increasing regulations on SO_x during the last decades, including implementations of scrubbers on industries and powerplants as well as removal of Sulphur from fuel has resulted in substantial decreases in SO_x levels. The current health impact of SO_x in Sweden is therefore low. For NO_x and O_3 the levels remain elevated in Sweden.

1.1.2 Particles

Solid air pollutants are classified according to size. All particles with a diameter of less than 10 µm are categorized as PM_{10} and this category includes all particles believed relevant for potential health effects. The largest particles, often referred to as coarse particles ($PM_{10-2.5}$), with a diameter size between 10 and 2.5 µm are mainly composed of parts of crustal materials such as salt, soil or dust from vehicle or road wear, but are also a product of natural sources such as dust storms. Coarse particles are mainly deposited in the upper bronchial tree of the lungs. Due to their relatively large mass, course particles usually do not disperse over large areas but stay relatively close to emission

sources, with the main exception being desert dust that can travel very far during favorable wind conditions.

Particles with a diameter less than 2.5 µm ($PM_{2.5}$) are classified as fine particles. Main sources comprise of direct emissions from combustion processes of either fossil fuels or organic material and secondary formation of $PM_{2.5}$ from precursor emissions such as SO_2, NO_x and VOC. $PM_{2.5}$ can disperse over a large geographic area, depending on meteorological conditions. Fine particles are deposited in the distal bronchiole and the smallest portion of the particles can enter the alveoli and blood stream.

Ultrafine particles ($PM_{0.1}$) with a diameter of less than 0.1 µm are also mainly produced through combustion. These particles are believed to be the most reactive species with large surface to volume ratios and possible entry into the alveoli and bloodstream.

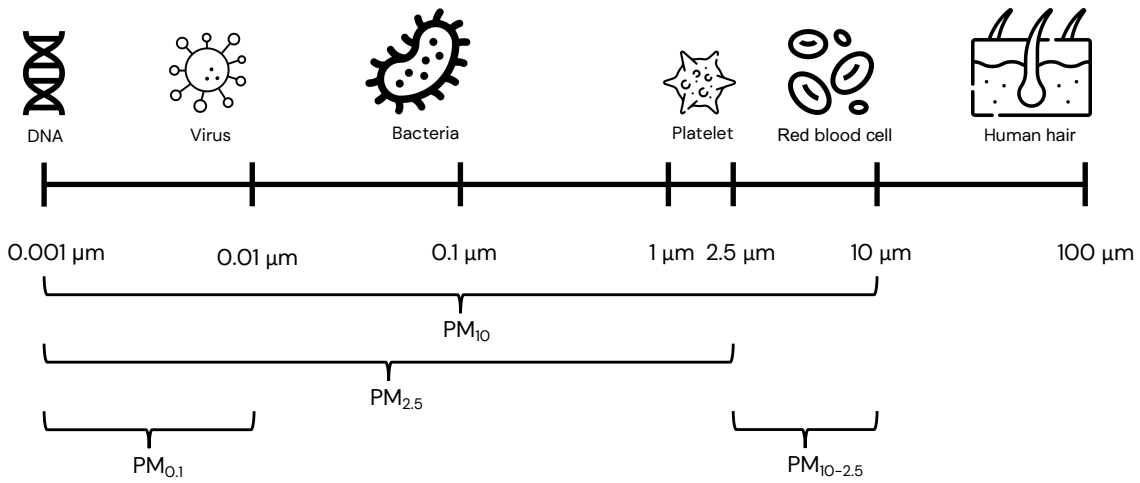


Figure 1. Size comparison of particulate matter. Scale is logarithmic.

1.1.3 Current air pollution regulations and guidelines

Table 1. is a summary of current European Union (EU) air quality standards and WHO air quality guidelines. The EU air quality standards are under revision and are suggested to be lowered but to the level of the current WHO guidelines (10).

Table 1. Current air quality directive from the European Union and guidelines from World Health Organization.

		European Union		World Health Organization	
Pollutant	**Averaging period**	**Limit values**	**Permitted annual exceedances**	**Guidelines**	**Permitted annual exceedances**
Fine particles ($PM_{2.5}$)	24 hours	n/a	n/a	15 µg/m^3	3-4 days
	1 year	25 µg/m^3	n/a	5 µg/m^3	n/a
Particulate matter (PM_{10})	24 hours	50 µg/m^3	35	45 µg/m^3	3-4 days
	1 year	40 µg/m^3	n/a	15 µg/m^3	n/a
Ozone (O_3)	8 hour mean[a]	120[b] µg/m^3	25 days[c]	100 µg/m^3	3-4 days
	Peak season[d]	n/a	n/a	60 µg/m^3	n/a
Nitrogen dioxide (NO_2)	1 hour	200 µg/m^3	18	n/a	3-4 days
	24 hours	n/a	n/a	n/a	3-4 days
	1 year	40 µg/m^3	n/a	n/a	n/a

[a] Maximum 8-hour mean per 24 hours

[b] Target value

[c] Averaged over 3 years

[d] Average of daily maximum 8-hour mean O_3 concentration in the six consecutive months with the highest six-month running- average O_3 concentration.

1.1.4 Air Pollution exposure assessment

It is not feasible to monitor every study participant's individual air pollution exposure in large epidemiological studies, both because of economic reasons but foremost because of the general retrospective nature of epidemiological studies. This results in a need for using modelling for exposure assessment. Additionally, ambient levels, and not personal exposure, are monitored and regulated in air quality guidelines worldwide, making ambient levels an important indicator to study to better inform and design future regulations.

The first and still widely used approach for exposure assessment is using measurements from fixed monitoring stations and assigning exposure based on ambient levels at the closest monitoring site or by averaging between several monitors. This approach has the advantage of being relatively easy to conduct, requires no information on the participants specific addresses and little to no modelling. The results from fixed monitoring data are usually robust and there is evidence to support that the they accurately reflect temporal variations in short-term air pollution levels over large spatial areas (e.g. cities) and are strongly correlated to personal temporal variability in exposure (11). Over the years other modelling techniques, i.e. land-use regression, dispersion and chemical transport models, and satellite models have emerged. These models aim to better capture the spatial component in the exposure variability.

In short, dispersion and chemical transport models try to model the dispersion of air pollutants concentrations from emission sources to receptor points using deterministic

approaches. The models can produce temporal and spatial output with varying degrees of resolution. However, dispersion models are not based on measured levels of ambient air pollutants but rely on theoretical assumptions on atmospheric processes and chemical reactions, using mathematical formulas (12).

Land-use regression models are statistical regression models that relate air pollution observations from a limited number of monitors to land-use variables in order to estimate spatial distributions of air pollution levels over a defined area. Statistical associations between land-use variables, such as proximity to roads, road density or industries, and monitoring data are estimated and then used for prediction of air pollution levels at locations without monitors. Land-use regression models have mainly been used for spatial modelling but in the recent years temporal covariates have been incorporated in the models to also model the temporal variability (12).

Satellite data derived models use data from instruments onboard sun-synchronous satellites with close to global coverage. The main product used is aerosol optical depth (AOD), a measure based on the reflection and absorption of light by suspended particles in the atmosphere. The AOD is proportional to the total amount of particles in the column of air between the ground and the sensor on the satellite. In theory daily AOD data is available all over the world with a high spatial resolution but in practice cloud coverage and the interference of large bodies of water introduce a lot of missing data. Furthermore, the association between the number of particles in the column of air between the ground and the satellite instrument does not necessarily reflect ground levels and the relationship is affected by weather and atmospheric conditions (13).

In recent years hybrid or ensemble models have been developed combining several or all of the above-mentioned methods of exposure assessment in an attempt to capitalize the strength from the different approaches. The models often use advance machine learning techniques to produce a model with a high temporal and spatial resolution trained on monitoring data (14, 15).

1.2 Ambient Temperature

Ambient temperature refers to the temperature in the ambient environment that people are exposed to. In a temperate climate with defined seasons, as is the case of Sweden, temperature varies considerably over the year. Apart from the long-term variability there is a substantial day-to-day variability and to a lesser extent an hour-to-hour variability. Further, there is a clear spatial variability of temperature.

Measurements combining ambient temperature and other metrological factors such as relative humidity, wind, and solar radiation are considered to be more accurate in reflecting the burden on the human body (16). However, it is unclear if these more complex measures better predict the risk of temperature related mortality and no

individual temperature measurement has been unequivocally proved superior to another, regarding the relationship to daily mortality (17, 18).

1.2.1 Ambient temperature exposure assessment

Measurements of ambient temperature have been ongoing for centuries with one of the longest still running time series of daily temperature started by Anders Celsius 1722 in Uppsala, Sweden (19). The most common way of estimating personal exposure to ambient temperature is by using measurements of ambient temperature levels at a nearby location as proxy. This approach has a high validity for capturing short-term changes on hourly or daily levels as the spatial variation of temperature over a geographical area is small. However it comes with the limitation of not being able to capture smaller local changes in temperature (e.g. the urban heat island effect) (20).

Apart from ground station monitoring there has been development in the use of satellite products (land-surface temperature) for estimation of ambient air temperature over larger geographical areas without extensive local measuring stations. Recent efforts in exposure assessment for epidemiological studies have used an ensemble machine learning approach similar to air pollution assessment. These models combine satellite products (land-surface temperature, measures of greenness, impervious surfaces, and light at night) with other spatial parameters (land use, climatic zone, population density and elevation) to train the model on available monitoring data. The model can then produce spatial and temporal estimates of ambient temperature levels over large geographical areas (21).

1.3 Cardiac Arrhythmias

1.3.1 Out-of-hospital cardiac arrest

Out-of-hospital cardiac arrest, hereafter referred to as cardiac arrest, is defined as the acute cessation of cardiac mechanical activity outside of a hospital setting. It is one of the leading causes of death in Europe and North America (3). The annual incidence of Emergency medical services (EMS)-treated cardiac arrests in Europe is estimated to about 275,000 (22), and the global incidence rate has been estimated to 83 per 100,000 person-years (3). Approximately 6,000 cardiac arrests occurred in Sweden in 2019. The 30-day survival after cardiac arrest has nearly doubled over the past two decades but is still at just below 11% in Sweden (23), similar to the rate reported in Europe (22).

1.3.1.1 Pathophysiology and risk factors of cardiac arrest

The typical sequence of electrical events in cardiac arrest is ventricular tachycardia degenerating to ventricular fibrillation and later to asystole. Electrical disturbances such

as polymorphic ventricular fibrillation and torsade de pointes are more common in patients without previous myocardial infarction or congestive heart disease (24).

Approximately 80% of cardiac arrests are related to ischemic heart disease either from an acute thrombotic event or related to an anatomical substrate (scarring from previous myocardial infraction). To a lesser extent the cardiac arrest could result from a cardiomyopathy or ion-channel defect, valvular disease, or congenital heart diseases (24, 25). Ischemia is considered the most common triggering factor of cardiac arrest, but cardiac arrests can also be triggered by systemic metabolic and hemodynamic alterations, neurophysiological factors and exogenous effects. A few triggering factors of cardiac arrest have been studied, including transient ischemia, electrolyte disturbances, physical exercise, substance abuse and emotional stress (24, 26, 27). Recent efforts have focused on environmental triggers such as ambient fine particles and ambient temperature (28, 29). The triggering mechanism can in turn interact with the underlying pathophysiological increased risk of for example ischemia, anatomical substrate or ion channel deficiencies (24, 25).

1.3.2 Atrial Fibrillation

Atrial fibrillation is the most common cardiac arrhythmia in the adult population with a prevalence of 1-3% (30, 31). The prevalence increases drastically with age and in the elderly population, above 75 years, the prevalence may be as high as 12% (32). With the ongoing demographic shift, with an aging population, the prevalence is expected to increase substantially (4). Atrial fibrillation is associated with increased mortality (33), dementia (34) and reduced quality of life (35). Further, approximately 20-30% of all strokes are attributable to atrial fibrillation (36, 37).

1.3.2.1 Pathophysiology and risk factors of atrial fibrillation

Atrial fibrillation is a disturbance in the electrical signaling in the atria of the heart resulting in irregular and often rapid heart rate. The atrial fibrillation is initiated in ectopic foci in the atria and is transmitted through the atrioventricular node to the ventricles (38). The underlying pathophysiological mechanism for developing atrial fibrillation is a progressive remodeling of the atria, resulting in disturbed electrical properties with reduced atrial repolarization periods and a reduced refractory phase. These changes to the atria increase the risk for recurrent arrhythmias and prevent normal sinus rhythm. The remodeling is believed to be driven by increased calcium levels, inflammation and deposition of fatty acids that result in development of atrial fibrosis (39-41)

The development of atrial fibrillation is multifactorial and known medical conditions with increased risk include several cardiovascular diseases, mainly heart failure, valvular disease, myocardial infarction, hypertension as well as metabolic disease such as diabetes mellitus, obesity and obstructive sleep apnea. Further thyroid dysfunction and

renal failure are associated with an increased risk of atrial fibrillation (41, 42). There is also evidence to support a triggering effect or increased risk from lifestyle factors, including high alcohol consumption, extreme levels of physical activity, physical inactivity and smoking (42).

1.3.3 Environmental exposures and Health

1.3.3.1 Air pollution and Health

Ambient air pollution exposure is associated with increased mortality and morbidity (43, 44). Recent estimates attribute 6.7 (8) million deaths to ambient air pollution globally, foremost related to cardiovascular disease, respiratory disease and cancer (45). The strongest associations have been observed for respiratory diseases, but the greatest burden is attributed to cardiovascular disease due to the high prevalence in the general population (8). In Sweden 7,800 deaths were contributed to air pollution exposure in 2018 (9). Traditionally health effects of air pollution have been divided into long-term and short-term effects. Long-term exposure meaning months to years of elevated exposure and resulting in increased mortality and various health outcomes (46). Short term exposure is measured in hours to days and the transient increased levels have been showed to be associated with increased incidence of all-cause mortality (43) and with cardiovascular outcomes such as myocardial infarction (47) and stroke (48).

1.3.3.2 Temperature and Health

There is a well-established link between ambient temperature and mortality (49, 50). The relationship is usually described as J, V or U shaped with an optimum temperature with low temperature-related mortality and with increased mortality for both warmer and colder temperatures over and under the optimum temperature range (50). The strongest relative risks have been associated with heatwaves and cold spells (51, 52) but the largest burden of temperature-related mortality is related to the extensive exposure to less extreme temperature deviations from the optimum temperature (50). The optimum temperatures, however, differ across geographical areas and cities (53, 54), so that e.g. while a given temperature level may be an optimum temperature level for Bangkok, in Stockholm this temperature may be associated with an increased mortality (50).

The increased mortality with non-optimum temperatures consists mainly of increased mortality from cardiovascular disease, pulmonary disease, diabetes and kidney disease (8, 55). Recent estimates attribute 1.9 million deaths annually to temperature exposure globally (8).

1.3.3.3 Climate change

The Intergovernmental Panel on Climate Change (IPCC) states in its latest report that global temperatures have risen 1 degree above pre-industrial levels and the warming is predicted to continue during the coming decades without drastic interventions (56). The emission of greenhouse gases is highly correlated to air pollution emissions with the main anthropogenic sources being the same, i.e. industries, traffic, agriculture and powerplants (57). Global warming, temperature exposure and air pollution are further interconnected as global warming is predicted to increase extreme weather events resulting in more frequent heatwaves and cold spells (58). Increased temperature has also been showed to increase the vulnerability to air pollution exposure (59), and the combined exposure to heatwaves and extreme air pollution levels might have substantial impact on health (60).

1.3.4 Air Pollution and Cardiac Arrest

The last two decades have seen an emerging body of evidence for the association between ambient air pollution and cardiac arrest. The exact relationship and significance of different pollutants are insufficiently studied but several studies have observed association between different air pollutants and cardiac arrest (59, 61-76). In 2017 a systematic review and meta-analysis was published by Zhao et al. observing significant associations for $PM_{2.5}$, PM_{10}, O_3 and NO_2 (29). A recent large case-crossover study from Japan confirmed the findings for $PM_{2.5}$ with a 1.6% increase of cardiac arrest risk per 10 microgram/m^3 increase in $PM_{2.5}$. However, the study did not observe any significant association for NO_2 (77). A few studies have found more pronounced risk estimates for the elderly (72, 76), men (66) and with previous medical condition such as heart disease or diabetes (76) signifying potential susceptible subgroups.

1.3.5 Ambient Temperature and Cardiac Arrest

There is a clear association between ambient temperature and cardiovascular mortality with increases in mortality from both short-term exposure to hot and cold temperatures (50, 54, 78). The category of cardiovascular disease is heterogeneous and the evidence for specific cardiovascular diagnoses are less clear. A few studies have demonstrated an association with increased cardiac arrest with both increased and decreased temperature from an optimum temperature in a U- or J-shaped association. As with all-cause mortality the optimum temperature varies between regions. The studies have applied either a case-crossover model (79-81) or a time-series approach (74, 82-86) for investigating short term effects. Usually, the investigated exposure windows range from 1 day to about 3 weeks. A few studies have used extreme temperatures as exposure, defined differently in the different studies but for example the 98th percentile of daily temperatures (84), with significant and more pronounced associations for both extreme cold and hot temperatures (80). A few studies have observed increased risks for the

elderly population (79) and for patients with hypertension (82) but the results are inconclusive with other studies showing no effect modification by age or previous medical conditions.

1.3.6 Air pollution and Atrial Fibrillation

The association between air pollution and ischemic events, i.e. myocardial infarctions and stroke, have been well studied and showed repeated positive associations (44, 47, 48). Some evidence suggests a similar association for heart rhythm disturbances, but it is less conclusive (87-89).

The majority of studies investigating air pollution and atrial fibrillation have done so by looking at short-term exposure. The methodology differs somewhat between different studies but predominantly designed as either time-series studies (90-94) or case-crossover studies (47, 95-100). All studies have used exposure data from fixed monitoring stations. The main outcome has been administrative hospital admission data (47, 92-96, 99) with a few exceptions of electrocardiogram (ECG) collected at hospitals (90) or data from populations with implantable cardiac devices, i.e. pacemakers, implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) devices (91, 97, 98, 100). There is some evidence of an association between different air pollutants and atrial fibrillation with the majority of published studies observing positive significant associations for particulate matter (90-94, 96-98) and a few for NO_2 (47, 93-95) or O_3 (100) while a few studies did not show any association between air pollution and atrial fibrillation (99, 101). The mixed results may partly be due to studies using hospital administrative data that are prone to considerable temporal misclassification since the timing of atrial fibrillation onset is difficult to establish. In many cases this leads to considerable bias towards the null hypothesis of no association or underestimation of the association (102). Furthermore, studying hospital administrative data will mainly include symptomatic cases requiring hospital care and not asymptomatic atrial fibrillation cases (reported to make up approximately one third of all cases) (103).

A few studies mentioned above have attempted to investigate associations between short term exposure of ambient air pollution and atrial fibrillation in specific patient populations with continuous ECG monitoring. A study in patients with single lead implantable cardioverter defibrillators designed to study ventricular arrhythmias also demonstrated associations between exposure to $PM_{2.5}$ and rapid atrial fibrillation (100). In a follow-up study of rapid and normo-frequent atrial fibrillation in patients with ICDs, higher 2-hour average $PM_{2.5}$ was associated with an approximate 25% higher risk of atrial fibrillation per interquartile range increase in exposure (98). Recent studies in Taiwan and Italy have shown similar results with increased risk of atrial fibrillation with increased particulate matter levels in device patients (91, 97). The main advantage of utilizing data from patients with cardiac devices is the temporal resolution of episodes of atrial

fibrillation and the ability to investigate asymptomatic episodes. The drawback is the selected study population with a population with greater cardiovascular burden and therefore results may not be as generalizable to the general population.

The evidence for long term exposure to air pollution and atrial fibrillation incidence is limited. A large Danish cohort study and a study on the Women's health initiative cohort showed a positive association between NO_2 exposure and atrial fibrillation but did not see an association for PM (104, 105). Stockfeldt et al. did not observe any association between air pollution and atrial fibrillation in a Gothenburg cohort (106). A recent large cohort study from Ontario, Canada including almost 5 million participants showed increased risk of atrial fibrillation incidence for both particulate matter exposure and O_3 (107).

1.4 Potential pathophysiological pathways for temperature and air pollution on health

1.4.1 Air pollution

The mechanisms by which air pollution effects cardiovascular disease are complex and still under investigation. Current evidence is derived from both animal models and experimental studies in humans. The primary effects of air pollution have been divided into three main pathways: (1) local effects in the lungs by oxidative stress and inflammation, (2) transduced systemic effects from the lungs by biological intermediates and (3) translocation of ultrafine particles with direct biological effects in remote deposition sites. All three of these initial pathways may then lead to secondary effect, with some level of independence but with substantial cross-reactions and overlap. Commonly the secondary effects are divided into six different overarching categories: (1) autonomic imbalance with increased sympathetic tone via afferent pathways from the upper airways of the lungs, (2) endothelial dysfunction, (3) systemic inflammation mediated through both the innate and adopted immune system, (4) prothrombotic pathways with increased platelet activation and alteration in plasminogen activation, (5) effects on the central nervous system, both direct effects on metabolism and on the hypothalamic-pituitary-adrenal axis activation and (6) epigenomic effects with changes in methylation. The interplay between the suggested pathways is believed to be complex but converge with increased cardiovascular risk, with both sub clinical disease and clinical events as a result. The importance of the different pathways may differ between cardiovascular outcomes, for different air pollutants and with short-term and long-term exposure to air pollution (44, 108).

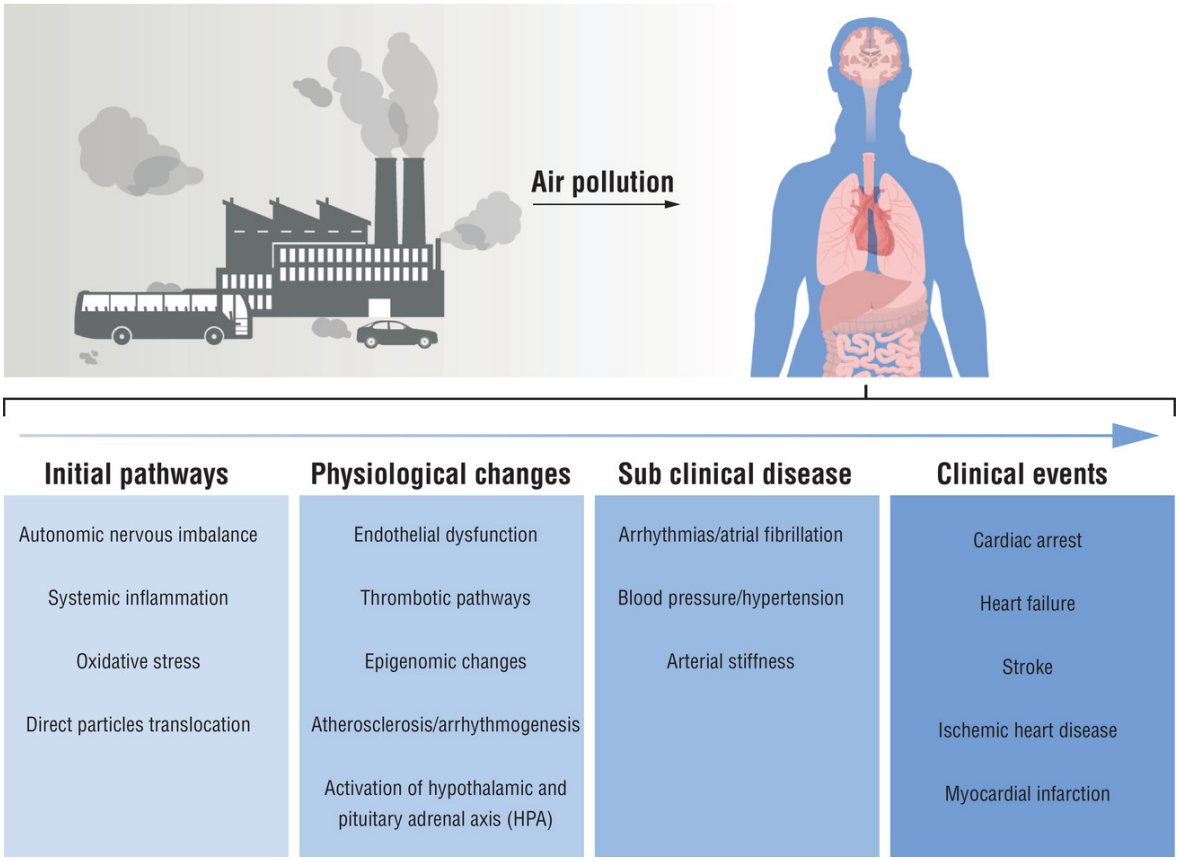


Figure 2. Potential biological pathways connecting air pollution and cardiovascular disease. *Jeroen de Bont, Suganthi Jaganathan, Marcus Dahlquist, et al. Ambient air pollution and cardiovascular diseases: An umbrella review of systematic reviews and meta-analyses © 2022 The Authors. Journal of Internal Medicine published by John Wiley & Sons Ltd on behalf of Association for Publication of The Journal of Internal Medicine.*

1.4.2 Temperature

The exact mechanistical pathways for the harmful effect of temperature exposure are not completely clear but several different potential mechanisms have been studied. For cold exposure the main pathways are: (1) Temperature effects on thermoreceptors in the skin that causes central nervous system alterations, with increased sympathetic tone and decreased heart rate variability (109, 110), (2) temperature induced changes in the renin-angiotensin system with elevated angiotensin-II levels in plasma (111), and (3) endothelial dysfunction and subsequent damage to the cardiomyocytes through intermediary proteins, e.g. plasma endothelin (16, 111). (1) and (2) both could lead to elevated blood pressure and increased cardiovascular disease risk. It is further observed that cold temperature is associated with risk markers of cardiovascular disease, i.e. low-density lipoprotein (LDL) level, fibrinogen levels, C reactive protein and platelet count (112-114). These factors might be intermediary markers for increased cardiovascular disease risk through inflammation and increased thrombus formation. The harmful effects of heat exposure are suggested to be due to increased skin blood flow and dehydration with increased blood viscosity and diminished pre- and afterload (16, 115).

Heatstroke has been shown to increase systemic inflammation and oxidative stress which in turn could lead to cardiovascular outcomes (16, 116).

1.5 Research gaps

There is a growing body of evidence suggestive of a harmful effect of both ambient temperature exposure and air pollution on health. The association to cardiovascular disease has been studied extensively. However, a potential association to arrhythmic diseases such as atrial fibrillation and cardiac arrest is less well understood and insufficiently studied. There is suggestive but no convincing evidence of an association between moderate changes in temperature and cardiac arrest. The absolute majority of previous studies investigating air pollution and arrhythmias have been conducted in areas with relatively high air pollution levels above current levels in Sweden. There is emerging evidence of harmful effects on health already at very low levels of air pollution and there is a knowledge gap of whether this is the case for arrhythmic diseases as well. The limited number of studies investigating air pollution exposure and risk of atrial fibrillations mainly use hospital registries which do not include asymptomatic or silent cases and have diverging results, highlighting the need for studying this association in other populations and with other methods.

2 Research aims

The overall aim of this thesis was to investigate acute risk of cardiac arrhythmias related to ambient environmental exposures. The specific aims were:

- To investigate the association between short-term exposure to ambient temperature and risk of cardiac arrest
- To investigate the assocaition between short-term ambient air pollution and cardiac arrest in an area of relatively low air pollution levels.
- To in investigate a potential triggering effect of short-term air pollution exposure on atrial fibrillation epiosodes, both in a general elderly population and in a population with patients with intracardiac devices.
- To investigate potential groups more suscepitble to the harmful effects of temperature and air pollution exposure

3 Materials and methods

3.1 Study Populations

3.1.1 Swedish Registry of Cardiopulmonary Resuscitation (Study I and II)

Study I and II use data from the same national registry of EMS-treated cardiac arrests. The registry is called the Swedish Registry of Cardiopulmonary Resuscitation (SRCR) but was formerly called the Swedish Cardiac Arrest Registry. The registry is filled out by EMS-personnel in case of a cardiac arrest dispatch. The registry started in 1990 with just a few ambulance stations and have grown to now include all ambulance dispatch centers and almost all EMS treated cardiac arrest in Sweden (117). The registry is based on the Utstein criteria (118) and include several variables of interest to the studies in the thesis such as: information on time of arrest, location, initial rhythm as well as information on ambulance dispatch time, drive time, given treatments and outcome. For Study I cases with presumed cause other than cardiac, including non-medical cases were excluded. The coding in the registry changed between Study I and II so for Study II all cases with a clear external cause, i.e. non-medical, were excluded.

3.1.2 STROKESTOP I and II (Study III)

Study III used data from the STROKESTOP I and II studies (119, 120). The STROKESTOP studies were atrial fibrillation screening studies where 75-year-olds in Stockholm and Halland underwent 2-week ambulatory ECG screenings with a handheld single lead ECG. A random sample from the population was invited and all participants without known atrial fibrillation had a baseline ECG and at least 2 weeks of screening with 2-4 measurements daily. The main purpose of the STROKESTOP studies was finding atrial fibrillation and start anticoagulant treatment with the hope of reducing stroke incidence compared to a non-screened control group. For Study II we included participants in Stockholm that had at least one episode of atrial fibrillation during the 2-week screening period. Atrial fibrillation episodes had to be preceded by two episodes of sinus rhythm to be included in the analysis. Covariates relevant to stroke risk, i.e. congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or transient ischemic attack (TIA), ischemic heart disease and body mass index (BMI), were collected and available for all participants.

3.1.3 Device Detected Atrial Fibrillation and Environmental Exposures (Study IV)

We recruited participants for Study IV at the Arrhythmia outpatient clinic at Danderyd Hospital, Stockholm, Sweden. The patients were recruited at their regular clinical follow ups and then longitudinally followed within the framework of the scheduled clinical check-ups. Inclusion criteria were patients with a cardiac device able identify and record atrial fibrillation, age above 18, a diagnosis of paroxysmal atrial fibrillation and

written informed consent. Exclusion criteria were cognitive impairment and chronic/permanent atrial fibrillation. We utilized the cardiac device's ability to identify and store atrial fibrillation episodes and collected information on time of onset, duration, and atrial and ventricular rate for all episodes and when available, intracardiac electrograms (EGM). Each participant had to have at least one episode with a detected atrial fibrillation episode linked with a stored EGM to confirm correct device-diagnosed atrial fibrillation. We required detected atrial fibrillation episodes to be longer than 30 seconds and have an atrial rate faster than 200 per minute to be included in the analyses. Longer duration of device detected atrial fibrillation episodes are sometimes incorrectly divided into several shorter episodes by the device due to undersensing. To reduce the risk of this misclassification, we introduced an additional restriction that atrial fibrillation episodes had to be spaced by a period of at least 3 hours from the end of one episode until the start of the next. Monitor data for air pollution was only available for Stockholm and all episodes occurring during a time period that the participant stated that they were away for an extended period of time (more than 1 month) were excluded.

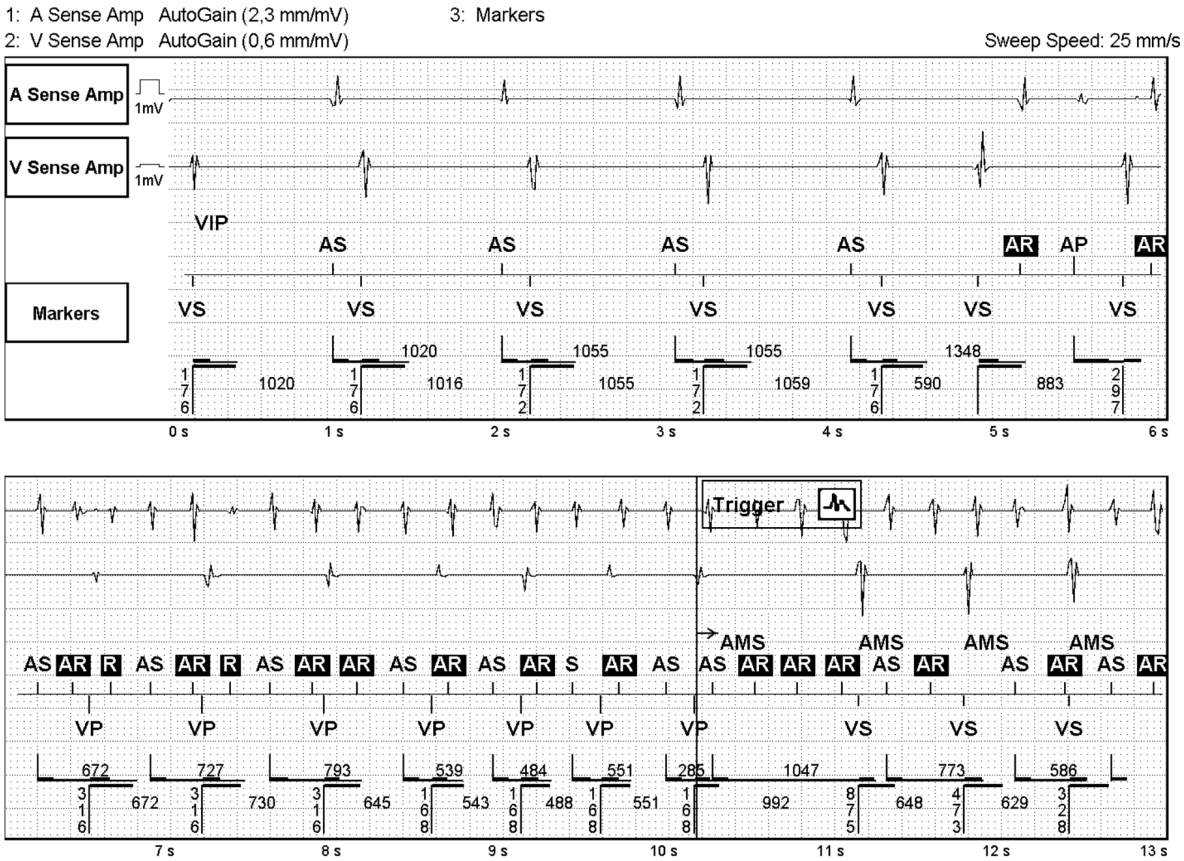


Figure 3. Intracardiac electrogram (EGM) from a patient with paroxysmal atrial fibrillation.

3.2 Environmental Exposure Assessment

3.2.1 Monitors

For Study I, III and IV air pollution measurements were collected from fixed roof-top monitors in central Stockholm placed to represent urban background levels. Temperature and relative humidity were collected form a suburban monitoring station approximately 8 km from the city center. The monitors are deployed and maintained by local authorities. Hourly measurements are recorded, the data is controlled and cleaned, and is thereafter publicly available retrospectively. We used the hourly means for the different exposures to create pre-defined exposure windows of interest.

For Study I we collected ambient temperature, relative humidity, PM_{10} and O_3 measurements. For Study III and IV we additionally collected $PM_{2.5}$ and NO_2 measurements. Temperature and relative humidity were measured at a suburban fixed site using a model 41 382 Relative Humidity/Temperature Probe platinum. PM_{10} and $PM_{2.5}$ measurements were performed using a Tapered Element Oscillating Microbalance instrument at roof-top level representing urban background levels. O_3 measurements were performed using a model O342 M Ozone analyzer and NO_2 measurements were preformed using a chemical luminescence method at the same monitoring site.

3.2.2 Models

For Study II we used a machine learning model for exposure assessment of daily $PM_{2.5}$, PM_{10}, O_3, NO_2 and temperature levels in a 1x1 km grid all over Sweden. The model combines satellite remote-sensing data (aerosol optical depth, land surface temperature, greenness, and light at night), information on land-use variables, air pollution sources as well as atmospheric models and data from fixed monitoring stations to predict air pollution and temperature levels using machine learning.

The geocoded address of pick-up for each case of cardiac arrest was assigned to the corresponding 1x1 km grid cell and daily air pollution levels were estimated for the case and control days for that location.

3.3 Statistical methods

In Study I, II and IV we made use of a case-crossover design with a time-stratified selection strategy (121). In this design all cases are matched with control period occurring on the same time, day of week, month, and year, resulting in 3-4 control periods per case. In this manner, each case serves as its own control and time invariant (or slowly varying) confounders are adjusted for by design. The association is then analyzed using conditional logistic regression and the results presented as Odds Ratios (OR) (Study I and IV) and percent change in relative risk calculated as (OR-1) x 100 (Study II).

In Study III we used generalized estimating equations (GEE) with robust standard errors to estimate population-level associations while taking into account the correlation among repeated measurements of the outcome within each study participant. GEE is a method for analyzing data collected in clusters where the observations within each cluster may be correlated and observations across different clusters are independent. The model allows for specifying the correlation structure for different responses and is considered to produce consistent results even with misspecified correlation structures as long as the main model is correctly specified.

For Study II, III and IV time-varying potential confounders were added to the main models for adjustment. Study II adjusted for ambient temperature modeled with two natural splines: one for lag 0-1 temperature (only for days above the median), aimed at capturing the immediate effects of high temperatures, and another for lag 0-4 temperature (only for days below the median) aimed at capturing the cumulative effects of low temperatures. For Study III we modeled temperature as a cubic spline with 4 equally-spaced knots to allow for a non-linear association, relative humidity modeled as a linear continuous variable, and weekday vs weekend and morning vs afternoon as indicator variables to adjust for potential temporal trends. Study IV adjusted for ambient temperature in a similar way to Study III and for public holiday as a dichotomous variable in the model.

We investigated different pre-defined exposure windows in the different studies. In Study II and IV we tested the robustness of the results and potential correlations between different exposure windows by using distributed lag models.

3.4 Ethical Considerations

The main ethical consideration for this thesis project is the collection and handling of personal data. Information regarding previous medical history, habits, and residential addresses could be sensitive and potentially intrusive and need to be handled accordingly. For all included studies the information was pseudoanonymized in the dataset and all analyses and results are presented on an aggregated level and in a way that information cannot be tracked to individual study participants. The datasets were kept on a secure server with limited access at Karolinska Institutet.

For Study I and II data was extracted retrospectively from the SRCR. The majority of patients included in the registry were deceased due to the low survival rate of cardiac arrest and informed consent would therefore strongly skew the inclusion to the registry, making it difficult to draw any general conclusions and the external validity would be low. Hence, people were included without their consent which must be considered a violation of their integrity. We have minimized the intrusion by analyzing the data anonymously on a group level. Study I and II are both retrospective studies investigating external exposures and did not interfere with the patient's regular care. There is no

individual gain for the people included in the study, but results will contribute to a greater understanding of cardiac arrest and thereby help to prevent new cardiac arrests in the future.

Study III used data from the STROKESTOP I and II studies. We did not collect any additional data to what was already collected as part of the STROKESTOP studies and had no effect on the participants treatment or health in any way. As with all the studies in this thesis the main ethical consideration was storing and analyzing personal data. To minimize the intrusion on the participants privacy all data was analyzed and presented on an aggregate level and all data was stored on a secure server only accessible to the study team.

In Study IV we recruited participants at their regular follow-ups at the arrhythmia open patient clinic at Danderyd Hospital. All participants gave written informed consent. We extracted information from the participants cardiac devices, i.e. pacemaker, ICD or CRT, something that is part of the regular follow up. We assessed that there is no increased risk for the participants and the extraction does not affect their treatment. The main ethical consideration is the collection and storing of personal data. As described above we minimized the risk by only analyzing aggregated data and storing all data on a secure server.

We believe that the actions above will minimize the risk of privacy violations and that the potential health benefits that the knowledge from this project will exceed the risks. We obtained ethical permits from the Stockholm regional ethics board or the Swedish ethical review authority for all four studies included in this thesis.

4 Results

4.1 Temperature and Cardiac arrest (Study I)

During 2000-2010 in Stockholm 11,480 EMS-treated cardiac arrests were registered in the SRCR. The analytic sample was 5,961 after excluding non-cardiac cases and cases where exposure data was missing. The mean age was 71 years and 67 % were men. Ambient temperature ranged from -18 to 25 degrees Celsius with a mean of 7.1 and an interquartile range (IQR) of 12.5. Ambient temperature was only weakly correlated with PM_{10} and O_3.

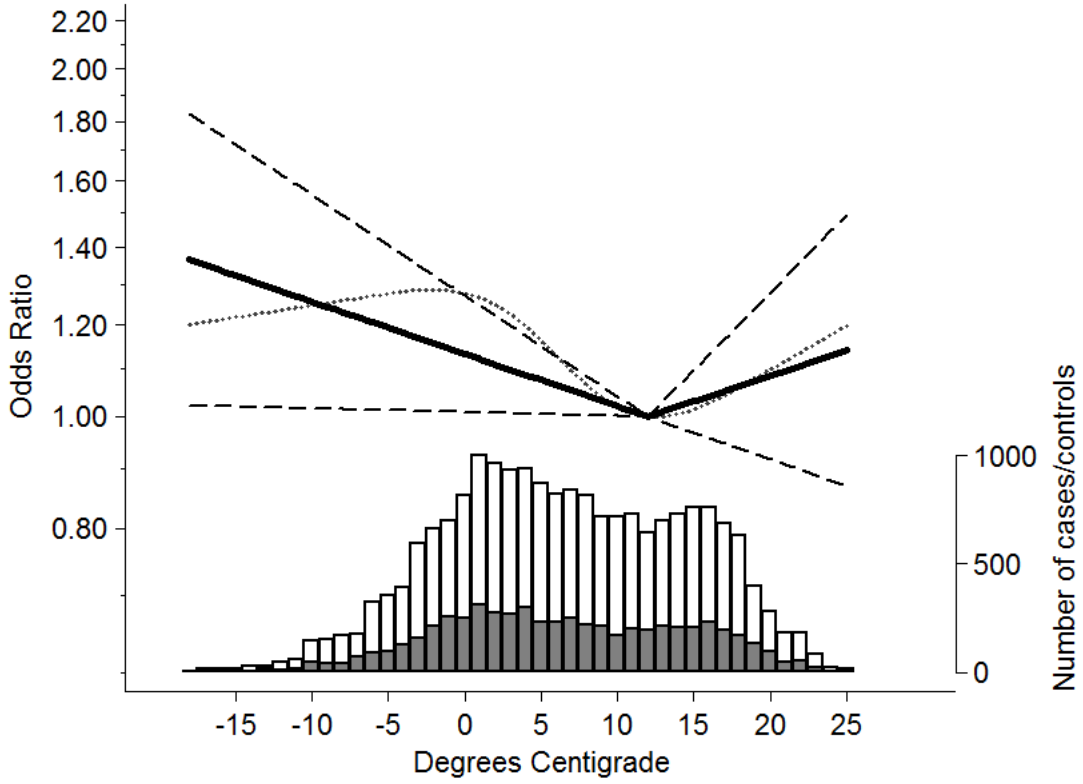


Figure 4. Association of preceding 24-hour mean ambient temperature and cardiac arrest. Restricted cubic spline model (dot) with four knots, piece-wise linear spline model (solid), with one knot set at 12 °C including confidence intervals (dash). The value of 12 °C was used as referent for the spline models. All estimates were obtained with a conditional logistic regression model. The odd ratio on left axis is plotted on the log-scale and the histogram describing the distribution of cardiac arrests cases (grey) and controls (white) by 24-hour mean ambient temperature. *Int J Hyg Environ Health, 2016, Jul;219(4-5):389-97. Reprinted with permission of Elsevier GmbH.*

We observed an increased risk of cardiac arrest with decreasing temperature from an optimum of around 12 degrees. For the 24-hour exposure window the odds ratio (OR) was 1.05, 95% confidence interval (CI) (1.00, 1.11) per 5 degrees decrease in temperature from a 12-degree optimum temperature (Figure 4.). We observed positive associations for the warm interval, but the association did not reach statistical significance. For the shorter exposure of 1 h prior to the cardiac arrest we observed somewhat stronger

associations in the cold interval (OR 1.07, 95% CI [1.02, 1.11] per 5 degrees decreased ambient temperature) below the optimum of 16 degrees. Overall, the association between ambient temperature and cardiac arrest took on a V or U shape, albeit with less certainty in the warmer interval.

Neither PM_{10} nor O_3 effected the association when added to the model for the cold interval. However, in the warm interval, with temperatures above 12 or 16 degrees respectively for 24h and 1 h exposure, the association to temperature was attenuated when we adjusted for O_3 by adding it to the model.

In secondary subgroup analyses we observed no significant associations by sex or age except for in the warm interval for the 1 h exposure. Here the cases with an age above the median of 71 years showed higher risk than the younger cases with a significant interaction. The OR in the warm interval was 1.15 95%CI (0.97, 1.36) per 5 degrees increase from the optimum temperature.

4.2 Air pollution and Cardiac Arrest (Study II)

We used national data from the SRCR between 2009 and 2019 for Study II. In total 29,604 cases of cardiac arrest met the inclusion criteria of being presumed medical, having a geocoded pick-up location and age above 18 years. The cases were distributed all over Sweden and with 63% of the cases occurring in municipalities defined as urban or peri urban. The mean age was 73 years, more than two thirds were male and 72 % occurred at home.

The machine learning model provided daily levels of air pollution for 1x1 km grids, and each case was assigned a grid cell based on the place of the cardiac arrest. The median daily $PM_{2.5}$ levels for the study population were 7.2 $\mu g/m^3$ with an IQR of 3.7 $\mu g/m^3$, and the PM_{10} levels were 13.7 $\mu g/m^3$ IQR (7.2 $\mu g/m^3$). We observed a north to south gradient of air pollution levels with highest levels in the south of Sweden.

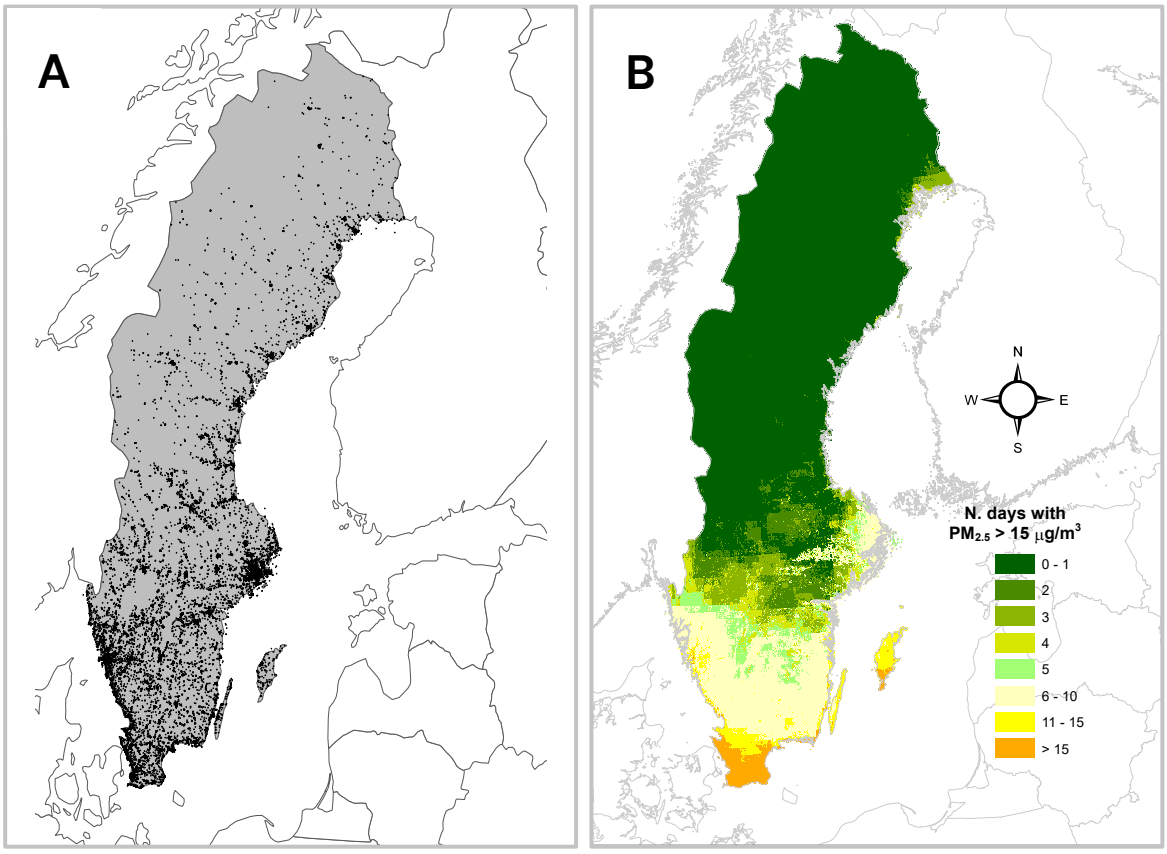


Figure 5. Distribution of cardiac arrest during the study period 2009-2019 with one dot per case (A) and days exceeding the WHO guidelines of 15 µg/m^3 $PM_{2.5}$ during 2015 in the study area (B)

We observed positive significant associations between $PM_{2.5}$ and PM_{10} and risk of cardiac arrest. The association appeared to be delayed with the strongest risk estimates for lag 4 (daily level 4 days prior to the cardiac arrest). For $PM_{2.5}$ the increased relative risk was 6.0 % (CI 0.9–11.3) per 10 µg/m^3 increase. We observed similar associations for PM_{10}. The levels of $PM_{2.5}$ and PM_{10} in our study population were highly correlated (correlation coefficient=0.8). We observed a positive but non-significant association for O_3 in lag 0 and a counterintuitive negative association for NO_2 (Figure 6). In a two pollutant with both NO_2 and O_3 the results became attenuated and non-statistically significant. In sensitivity analyses, all pollutants showed similar association patterns for both single lag and distributed lag models.

The national machine learning exposure model allowed for inclusion of cardiac arrest cases from all of Sweden. We tried to utilize the large dataset to investigate potential differences between younger and older patients and men and women but did not observe any clear differences or susceptible groups and no significant interactions. We investigated potential differences by urbanization and observed similar risk for cases occurring in rural and urban municipalities with a p-value for interaction of 0.89, suggesting that our observations are relevant even in non-urban areas.

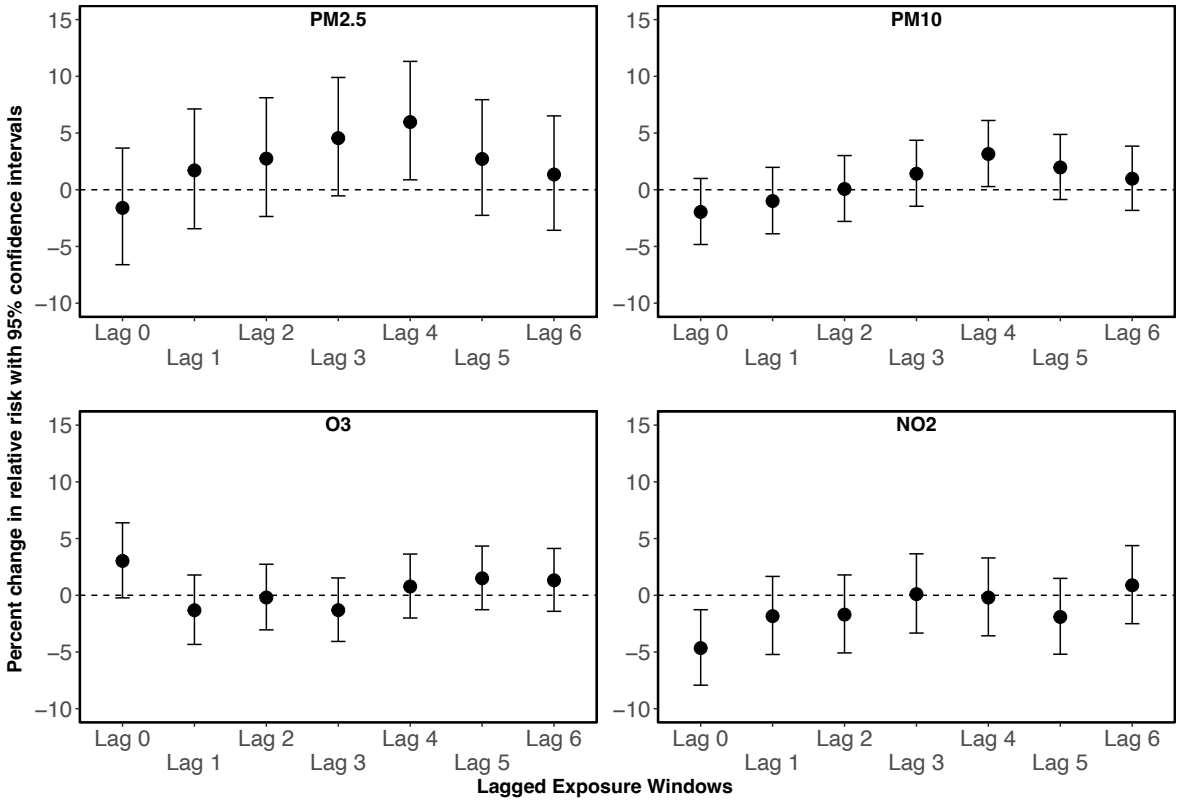


Figure 6. Association between daily lagged air pollutant exposure windows and cardiac arrest as percent change in relative risk per 10 μg/m^3 increase with 95% confidence intervals. Lag estimates are provided for same day (Lag 0) and each preceding daily average six days prior to event. $PM_{2.5}$, PM_{10}, NO_2 analyses included all days across all seasons while O_3 were restricted to spring and summer (Mars-September) only.

In the stratified analysis we observed stronger risk estimates for cases with first ECG rhythm of ventricular tachycardia (VT)/ventricular fibrillation (VF) compared to cases with asystole/pulseless electrical activity (PEA). The risk estimates were positive for all lags for VT/VF with the strongest estimates in lag 2 to lag 5. For asystole/PEA cases the pattern was less clear with no significant associations and not as pronounced risk estimates for the intermediate lags (lag 3, lag 4) compared to the VT/VF group despite including considerably more cases.

4.3 Air pollution and Atrial Fibrillation (Study III and IV)

4.3.1 Air pollution and atrial fibrillation in a general population (Study III)

In Study III we utilized data from to the two atrial fibrillation screening studies STROKESTOP I and II. In total 8,899 randomly selected 75- and 76-year-olds living in Stockholm were screened with one lead thumb ECG, 2-4 times a day for 14 consecutive days. Our analytic sample constituted of the participants with at least one recorded episode of atrial fibrillation preceded by two episodes of sinus rhythm. This resulted in 218 participants contributing 469 episodes of atrial fibrillation and 7 500 episodes of sinus rhythm. The median number of episodes was 1 with a range between 1-10 episodes. The patient characteristics are described in Table 2. The fixed single monitor

showed mean 24-hour levels of $PM_{2.5}$ of 4.6 (IQR 3.2) $\mu g/m^3$ and PM_{10} of 13.7 (IQR 7.8) $\mu g/m^3$ during the study period. $PM_{2.5}$ and PM_{10} was correlated (r=0.61) and PM_{10} and $PM_{10-2.5}$ was highly correlated (r=0.86).

Table 2. Study population characteristics from Study III and Study IV.

Characteristic	**Study III** n=218	**Study IV** n=91
Age, median (IQR)	75 (1)	78 (10)
Women, n (%)	106 (49%)	35 (39%)
Hypertension, n (%)	110 (51%)	54 (59%)
Ischemic heart disease, n (%)	25 (12%)	25 (28%)
Diabetes Mellitus, n (%)	24 (11%)	13 (14%)
Stroke or TIA, n (%)	19 (9%)	10 (11%)
Atrial fibrillation episodes per participant, median (IQR)	1 (2)	4(7)

Note: *IQR interquartile range, TIA transient ischemic attack*

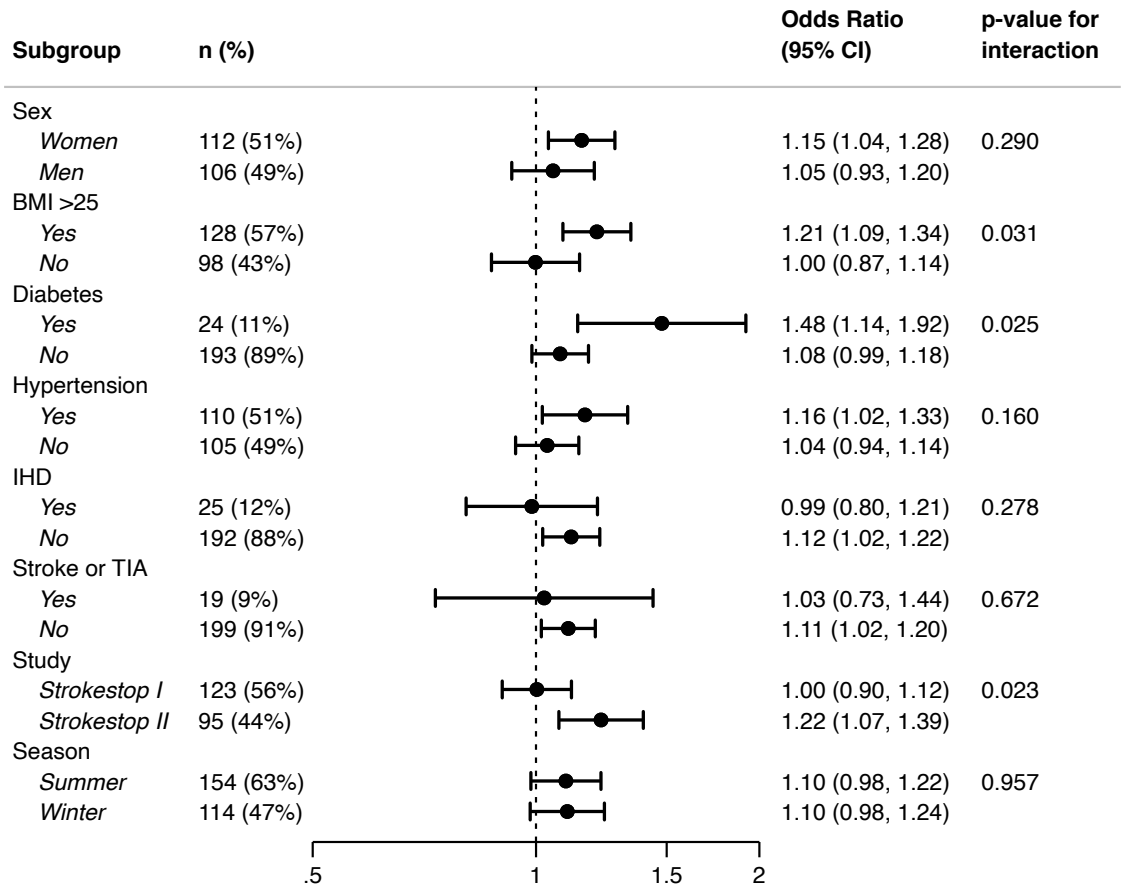
We observed increased risks of atrial fibrillation episodes with increased PM_{10} and $PM_{2.5}$ levels in the 12-24-hour exposure window. The association was more pronounced and statistically significant for PM_{10} with an OR of 1.10 (95% CI [1.01, 1.19]) per IQR increase. For $PM_{2.5}$ the association did not reach statistical significance. We further investigated the association between $PM_{10-2.5}$ and atrial fibrillation episodes and observed an association with the highest risk at 12–24-hour exposure. O_3 was positively associated with increased risk of atrial fibrillation with the most pronounced risk estimates for shorter exposure windows, but the association did not reach statistical significance. We did not observe any clear associations for NO_2.

In subgroup analysis we observed stronger risk estimates from $PM_{2.5}$ exposure for the small groups of participants with diabetes OR 1.48 95%CI (1.14, 1.92) and for participants with BMI>25 OR 1.21 95%CI (1.09, 1.34) both with significant p-values for interaction.

Table 3. Association of moving averages of air pollution levels and atrial fibrillation episodes scaled to the 24-hour interquartile range, adjusted for temperature, relative humidity, day of week and time of day.

Pollutant	**Moving Average**	**Odds Ratio**	**95% CI**
$PM_{2.5}$	12-24 hours	1.04	0.97, 1.13
PM_{10}	12-24 hours	1.10	1.01, 1.19
$PM_{10-2.5}$	12-24 hours	1.09	1.01, 1.17
NO_2	0-12 hours	0.97	0.87, 1.09
O_3	0-12 hours	1.13	0.97, 1.32

Note: *CI Confidence interval, $PM_{2.5}$ Particulate matter < 2.5 μm, PM_{10} Particulate matter < 10 μm, $PM_{10-2.5}$ Particulate matter 2.5-10 μm, Particulate matter < 10 μm, NO_2 Nitrogen dioxide, O_3 Ozone.*



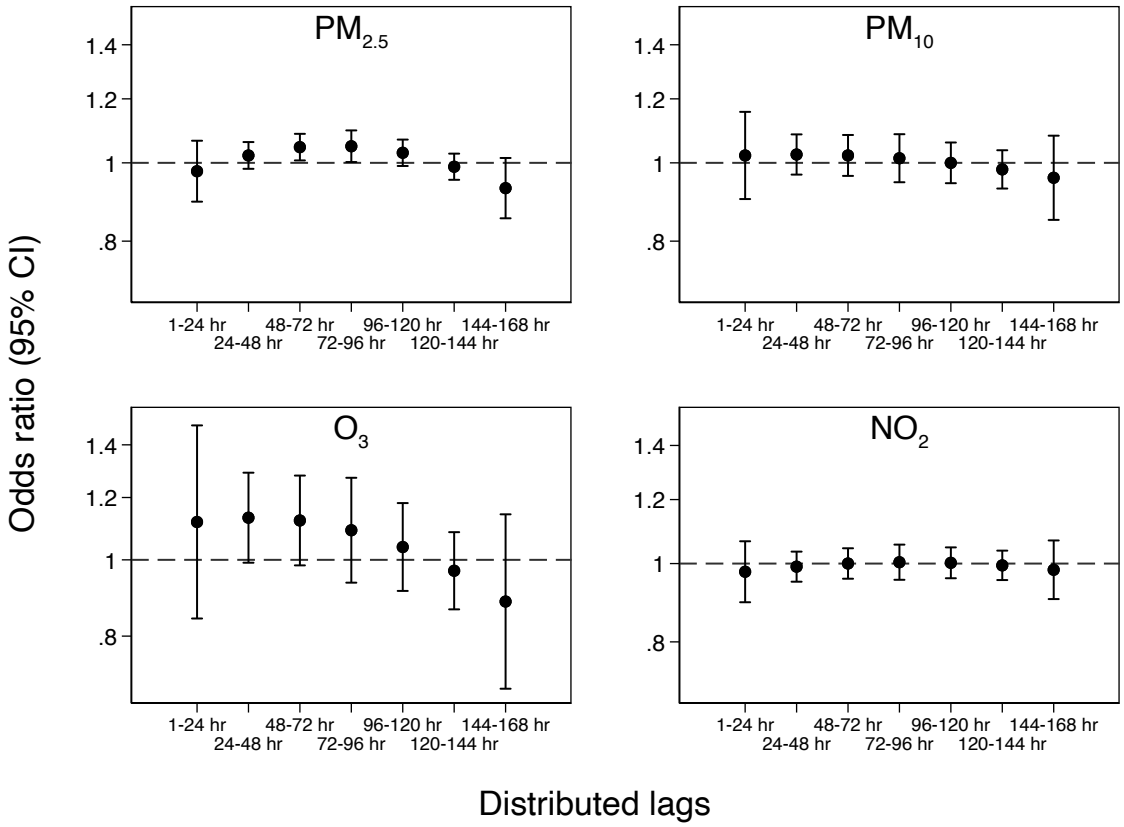
Note:. *PM_{10} Particulate matter < 10 micrometers, CI confidence Interval, IHD Ischemic heart disease, TIA Transient ischemic attack.*

Figure 7. Association of preceding 12–24 h concentrations of PM_{10} and atrial fibrillation episodes per interquartile range increase, adjusted for temperature, relative humidity, day of week and time of day for each subgroup with a multiplicative interaction test. *Environ Int. 2020 Aug;141:105765.* Reprinted *under the terms of Creative Commons CC-BY.*

4.3.2 Air pollution and atrial fibrillation in a population with intracardiac devices (Study IV)

We recruited a total of 125 participants with intra cardiac devices and paroxysmal atrial fibrillation rom Danderyd Hospital's Arrhythmia outpatient clinic and they were followed between 2017 and 2020. Participants with an atrial fibrillation burden of more than 30% and atrial fibrillation episodes with less than 3-hour time-gap were excluded, and this resulted in 584 episodes of atrial fibrillation from 91 participants for the analytic sample. The characteristics of the participants are presented alongside the participants of Study III in table 2 for comparison.

Air pollution data from the fixed monitor showed a mean $PM_{2.5}$ level of 4.7 $\mu g/m^3$ (IQR 3.6) and mean of 11.8 (IQR 9.3) for PM_{10} during the study period.



Note:. *$PM_{2.5}$ Particulate matter < 2.5 micrometers, PM_{10} Particulate matter < 10 micrometers, NO_2 Nitrogen dioxide, O_3 Ozone.*

Figure 8. Associations between air pollution levels and atrial fibrillation episodes with odds ratio and 95% confidence intervals for distributed lags of $PM_{2.5}$, PM_{10}, O_3, and NO_2 ranging from 1–24 hour to 144–168 hour per IQR change in air pollution levels ($PM_{2.5}$ = 3.6, PM_{10} = 9.3, O_3 = 28.3, and NO_2 = 6.2). O_3 analysis stratified to warm season. The association is adjusted for temperature as a cubic spline and public holidays as a dichotomous variable. *Environ Epidemiol. 2022 Jul 22;6(4):e215. Reprinted with permission from Wolters Kluwer Health, Inc.*

We observed an increased risk of atrial fibrillation episodes with increases in $PM_{2.5}$ levels. The association was delayed with the most pronounced risk estimate at a lag 48-72 hours and 72-96 hours prior to the atrial fibrillation episodes. We observed positive association for lag 24-48 hours and 48-72 hours for O_3 but it did not reach statistical significance. No clear associations were observed for PM_{10} and NO_2. The lagged associations are presented in figure 8. The observed associations were robust when excluding participants with more than 10% atrial fibrillation burden and the risk estimates for $PM_{2.5}$ became stronger when only including participants that lived closer than the median (15.5 km) from the monitor.

5 Discussion

As described in the introduction there is ample evidence of negative health impact related to ambient temperature and air pollution exposure. The studies presented in this thesis try to investigate how these environmental exposures might be connected to cardiac arrhythmias, conditions with an extensive health burden, and with a less clear relation to these exposures. A potential association would be relevant from both a mechanistical point of view as well as from a public health perspective. The studies presented are also conducted in settings with relatively low-moderate exposures in a global perspective. Potential associations in this low exposure environment are of relevance for current and future regulatory measures and mitigation strategies.

5.1 Environmental exposures and cardiac arrest (Study I and II)

In Study I and II we investigated if and how external environmental exposures, i.e. ambient temperature and air pollution, are associated with cardiac arrest. Using data from the national SRCR we observed associations for both ambient temperature and for particulate matter. In Study I ambient temperature was associated with cardiac arrest in a U or V shaped manner with an optimum temperature (temperature with the lowest risk of cardiac arrest) around 12 degrees. The association was statistically significant for temperature below the optimum temperature but not for temperatures above. This non-linear relationship is similar to several large studies investigating all-cause mortality (50) as well as corroborated by several studies investigating temperature and cardiac arrest in other study populations (79, 80, 122). The reason for non-significant associations in the upper temperature range in our study might be due to limited power with the relatively small sample size or might reflect a greater burden of cold related health effects in Sweden. Comparing these results to the subsample of Sweden in the study by Gasparini et al. from 2015 demonstrate a similar pattern for all-cause mortality in Sweden but with a somewhat higher optimum temperature (50). As discussed in the introduction section the optimum temperature appears to be different in different geographical areas and might differ for different outcomes (50, 53, 54). The differences may reflect several factors, including biological and behavioral factors as well as building characteristics such as air conditioning and heating (123, 124).

Mechanistically there is evidence to suggest a triggering effect of temperature on cardiac arrest. As discussed in the introduction short-term exposure to cold temperatures act as a stressor on the body and might introduce changes in the autonomous nervous system and cause inflammation. Our results suggest a rapid mode of effect, with associations even for 1 h temperature exposures, and this is more in line with changes in the autonomous nervous system (16). We observed more pronounced associations for cases with VT/VF compared with asystole and PEA, reinforcing that cold temperature might have a short-term potential pro-arrhythmic effect.

In Study II we investigated the association between ambient air pollution and cardiac arrest and observed positive and significant associations for $PM_{2.5}$ and PM_{10}. The association seemed to be delayed with the highest risk of cardiac arrest 3-4 days after PM exposure with no clear association for same day exposure. We observed this association even though the levels of particulates are low in Sweden and regardless of whether the cases occurred in a rural or urban area. These results suggest that there is a harmful effect of air pollution exposure even at levels below current regulations. Our results are in line with several previous studies conducted in areas with higher air pollution levels even though the lag structure between different studies differ somewhat, with some observing more direct associations with associations for the same day exposure (28, 64-67, 70, 72, 77, 125) and others a delayed association similar to ours (68, 71, 76). The timing of the exposure might still be unclear but the epidemiological evidence for PMs negative impact on cardiac arrest is growing.

The results for the gaseous pollutants were less clear. We observed positive but non-statistically significant associations for same day O_3 exposure during the spring and summer. These results are in line with significant associations observed in a meta-analysis from 2017 (29) and a few recent studies (75, 76). We observed counterintuitive negative associations for same day exposure for NO_2, but this was attenuated and no longer statistically significant in the two-pollutant model with O_3, perhaps partially due to their negative correlation as an expected consequence of O_3 being a secondary pollutant created from the reaction of NO_x and O_2 in the presence of sunlight.

The pathophysiological pathway that might connect air pollution exposure to cardiac arrest is not completely established. As discussed in the introduction there is evidence of PM having an adverse health effect by several different pathways including both inflammation, oxidative stress, changes in autonomic tone and hypercoagulability (126, 127). There is evidence of inflammation, oxidative stress, and autonomic dysfunction to promote ventricular arrhythmias, and this is a plausible pathway for air pollution effects on cardiac arrest. Animal studies have shown increased risks of premature ventricular contractions (PVC) (128, 129) and ventricular arrhythmias (128) with PM exposure. Further, both experimental and epidemiological studies in humans have reported that exposure to PM increases risk of PVCs (130), prolongs QT-interval (131) and are related to repolarization disturbances (88, 132), all ECG changes that might be precursors to ventricular arrhythmias. Several studies have shown increased risk of VT/VF episodes in patients with ICDs within hours of air pollution exposure (133, 134). Our findings in Study II suggested a lagged or delayed association more in line with an inflammatory cascade initiated by PM inhalation, but a clear pathophysiological pathway is still unclear and is probably multifactorial.

In summary, Study I and II contribute to the evidence of negative health impact on cardiac arrest of ambient environmental exposures. We observed significant

associations between cold temperatures and cardiac arrest in Stockholm in Study I. The associations were observed for temperatures below an optimum of 12-16 degrees Celsius. In Study II we observed significant associations between PM and cardiac arrest in all of Sweden even though the levels of air pollution were below current regulatory standards reinforcing the relevance of the new stricter WHO air quality guidelines.

5.2 Air pollution and atrial fibrillation (Study III & IV)

In Study III and IV our aim was to investigate the association between air pollution exposure and triggering of atrial fibrillation episodes. This was done in two different populations presenting different opportunities and potential limitations. For Study III we utilized data from a two large atrial fibrillation screening studies where the participants were examined with one-lead ECGs 2-4 times a day for 14 days. In this population of relatively healthy randomly selected 75-year-olds we observed a statistically significant association between PM_{10} exposure and atrial fibrillation episodes. We observed a similar positive association for $PM_{2.5}$ but the confidence interval included the null hypothesis. The highest risk was observed for the slightly delayed exposure of 12-24 hours. We observed similar results for $PM_{10-2.5}$ fraction compared with PM_{10} but the correlation between PM_{10} and $PM_{10-2.5}$ was high making differentiating potential effects challenging.

In Study IV we recruited participants with intracardiac devices at the arrhythmia department at Danderyd Hospital. In this selected population with more co-morbidities but with a close to continuous registration of heart rhythm disturbances we also observed associations between PM exposure and atrial fibrillation. For Study IV the highest risk was observed for $PM_{2.5}$ with a delay of 3-4 days with no association for shorter lags. As for Study III $PM_{2.5}$ and PM_{10} showed similar associations, which is expected given the high correlation between the two. In Study IV the association for PM_{10} did not reach statistical significance. The associations between PM and atrial fibrillation are in line with the evidence of some of the previous studies, with significant associations for $PM_{2.5}$ (91, 94, 97, 98) and PM_{10} or $PM_{10-2.5}$ (94, 97, 135).

The timeframe of the association differed between Study III and IV, where we observed a more direct association in Study III and a somewhat delayed association in Study IV. However, the study design of Study III with repeated measures over a 14-day period made investigating more delayed lags complicated and direct comparison between the two studies difficult. Previous studies have reported associations for both short and longer lags. Link et al observed direct associations with increased risks already after 2 hours (98) while Liu et al observed strongest risk for 24-hour exposure but significant associations up to 72 hours (97) for $PM_{2.5}$. For PM_{10} and $PM_{10-2.5}$ studies have shown both associations for same day levels as well as longer 3-day lags (94, 97, 135)

We did not observe any statistically significant associations for O_3 or NO_2 exposure and atrial fibrillation. However, we observed positive associations for O_3 in Study IV suggestive of an association. Several previous studies have investigated O_3 exposure and atrial fibrillation, and the majority have not observed significant associations (47, 92, 95, 97, 98). A recent meta-analysis did not find an association (136).

As previously stated, air pollution is believed to increase oxidative stress and have effects on the autonomic nervous system (126, 127). There is some evidence that suggests that both alterations in the autonomic nervous system and inflammation could in turn increase the risk of atrial fibrillation (137-139). Furthermore, a few studies of $PM_{2.5}$ exposure have observed increased risks of electrical disturbances in the atria such as p-wave complexity and PR duration, that are important ECG predictors of atrial fibrillation (140). However, a a conclusive pathophysiological pathway connecting air pollution and cardiac arrhythmias is still lacking (126).

In summary the findings from Study III and IV add to the evidence of a triggering effect of particulate matter on atrial fibrillation episodes both in a more general elderly population and in a patient population with intracardiac devices.

5.3 Susceptible subgroups

There has been a lot of efforts trying to uncover potential subgroups that might be more susceptible to environmental exposures. This has been done both to better understand the exposure-response relationship from a mechanistical point of view as well as with the hope of being able to suggest targeted interventions for certain groups. In the context of Stockholm and Sweden, the study area of the studies presented in this thesis, targeted interventions might have limited implications given that we observe associations even at low levels of air pollution and at temperatures close to the mean. Limiting exposure for certain groups would be difficult. However, mechanistically, investigating susceptible groups is of interest and importance.

5.3.1 Cardiac arrest

We had limited knowledge of co-morbidities in Study I and II as it is not collected in the SRCR and could only investigate potential differences regarding sex and age. We did not find any clear differences between men and women nor older and younger cases.

There is some evidence of a difference in susceptibility by age and sex in the literature regarding temperature exposure and cardiac arrest with a few studies observing increased risk in elderly and/or in men (79, 80, 84, 86). Previous studies on air pollution and cardiac arrest are inconclusive regarding susceptible groups. Two studies have observed increased risk for older individuals (66, 77) while two studies have observed stronger risk estimates for younger individuals (64, 72). Several meta-analyses on PM exposure and cardiovascular disease have observed increased risks for elderly people

(126) and it can be hypothesized that this might be a function of the gradual decline of biological and physiological processes with aging. This might reduce their resilience to air pollution exposure, but no specific potential pathophysiological pathway related to aging has been shown (126). It might be that Study II was underpowered to observe a difference given the low air pollution levels, but it is also possible that a potential biological susceptibility is counteracted by the fact that younger individuals might be more exposed if they spend more time outdoors. Similarly, there is no clear pattern from previous studies of a potential difference in susceptibility by sex with mixed results from several studies and only a few (64, 67) of the previous studies have observed increased risk for men and with wide confidence intervals and no test for interaction. There is still no clear evidence on potential susceptible groups with regards to the potential harmful effect of $PM_{2.5}$ exposure for cardiac arrest.

5.3.2 Atrial fibrillation

We observed higher risk of atrial fibrillation associated with PM exposure in participants with diabetes and overweight in Study III. Unfortunately, we could not corroborate this finding in Study IV due to the small study sample. The subgroup of participants with diabetes in Study III was small as well and the result needs to be interpreted with caution, but it did show higher risks and a statistically significant interaction. There is some evidence in the literature of increased risks of air pollution exposure for patients with diabetes and overweight (141, 142), and it has been hypothesized that this could be due to increased baseline inflammation and subsequent endothelial dysfunction (143). From a mechanistical point of view a susceptibility to air pollution by diabetes, overweight and the metabolic syndrome is of great interest and the potential interaction needs to be investigated further.

5.4 General discussion

5.4.1 Exposure to moderate changes in temperature

In Study I we observed associations between slight deviations from an optimum temperature and cardiac arrest, with the highest risk at the extremes but with a fairly linear association for the colder temperature interval. This is in line with several large multinational studies observing the highest relative risk of all-cause mortality with temperature extremes but the largest burden of cold related mortality from slight deviations from the optimum (50, 144). Given that both cold and warm temperatures seem to have a negative impact on health and that we cannot control outdoor temperature (apart from limiting greenhouse gas emission and thereby limiting global warming) a potential intervention is difficult. Potential mitigating efforts could be limiting personal exposure to temperature by use of air conditioning or cooling centers as well as well insulated housing with appropriate heating. Further, several communities have adopted extreme weather warning systems for notifying the public, e.g. of a potential

heatwave, but as to date the effectiveness of such interventions are unclear but merit further attention (145). Given the rapid associations observed in Study I such measures might reduce cases of cardiac arrest on very cold and warm days.

With a changing climate the future of ambient temperature exposure and extreme temperatures is unclear. According to the latest IPCC report Sweden should expect substantial increase in mean temperature by 2050. This might reduce the exposure to cold temperature but comes at the cost of more extreme temperature days that are associated with the highest relative risks. How this will affect the overall burden of temperature related mortality and morbidity in a temperate country as Sweden is still unknown, but recent evidence suggest that the optimum temperature might change with increasing temperatures due to adaptation (146). However, global warming is expected to result in more heatwaves that have been shown to be associated with substantial morbidity and mortality (147). The built environments in Sweden are poorly equipped to accommodate heat compared to cold (with buildings traditionally designed to retain warmth rather than expel it and limited air conditioning in homes and public buildings). Increased number and strength of heatwaves would have a substantial impact on health.

5.4.2 Air pollution exposure in low level areas

Air pollution levels in high income countries have been declining during the last decades and Sweden is one of the least polluted countries in Europe (148). In parts of the world air pollution levels remain high and is even increasing, with levels comparable to the catastrophic levels in Europe in the middle of the last century (149). As described in the introduction there is significant evidence of unhealthy or hazardous effects of these high levels both in the short-and long-term. As for exposures to low levels of air pollution the potential harmful effect is less clear, but recently several large studies have shown increased risks of all-cause mortality and cardiovascular outcomes even at low levels of air pollution (150). The accumulative evidence resulted in that the WHO presented new guidelines for ambient air pollution exposure in 2021. The WHO guidelines now states that an annual mean of 5 $\mu g/m^3$ is considered the target for $PM_{2.5}$ (151). The EU is currently revising its air quality guidelines but the present legally binding levels for $PM_{2.5}$ is 25 $\mu g/m^3$ (152). Study II, III and IV presented in this thesis are all conducted in a study area with relatively low levels of air pollution, clearly below the present EU standards and close to the new very low WHO guidelines. Despite this we observe associations between particulate matter exposure and cardiac arrhythmias. Our findings strengthen the hypotheses of no clear threshold or safe level of air pollution exposure with linear or super-linear exposure response relationships (150). This has an impact on regulatory considerations and need to be evaluated thoroughly in the future especially considering the large public health impact of cardiac arrest and atrial fibrillation.

The large public health impact of a potential association between air pollution and cardiac arrest is a consequence of the universal exposure to air pollution and the high incidence of cardiac arrest. The results from Study II in context with previous studies suggest that PM triggers cardiac arrest even at levels below the current regulatory standards. It is plausible that a reduction in $PM_{2.5}$ levels would decrease the incidence of cardiac arrest and thereby improve public health. How large of an impact on cardiac arrest incidence this would have, is not possible to conclude from this study nor from short-term studies in general. However our results are in line with previous evidence from large long-term studies suggesting that reductions in air pollution are associated with decreased mortality and increased life-span (153) and it is plausible that an important part of this association is driven by the potential association between air pollution and cardiac arrest.

Similar to cardiac arrest, the findings of an association between air pollution and atrial fibrillation also have an important impact on public health. Our results are suggestive of an association for triggering of atrial fibrillation and these results are corroborated by several other short-term studies (91-94, 96-98) and further by a few recent long-term studies investigating atrial fibrillation incidence (154, 155). Atrial fibrillation is one of the leading causes of stroke (36, 37), increases the risk of dementia (34) and is related to increased mortality and morbidity (33, 35). The public health expenditures related to atrial fibrillation is estimated to €708 million annually in Sweden; more than the total cost of diabetes or congestive heart failure (156). Population-level approaches geared towards primary prevention of this condition offer the potential for substantial public health gains. The observed associations, even at the comparatively low levels of air pollution exposure in Stockholm, Sweden, suggest that increased efforts at reduction in air pollution exposure might reduce cases of atrial fibrillation and decrease the disease mortality and morbidity.

5.4.3 Methodological considerations

The findings presented in this thesis must be interpreted in the context of some limitations and methodological considerations. First, all four studies in this thesis are investigating short-term associations. This can give valuable information on potential biological effects of the exposure and suggest harmful effects of exposure. However, short-term associations suggest triggering of an event by the studied exposure and this is not directly transferable to long-term effects of the exposure. It is plausible that negative short-term effects would translate into harmful effects with long-term exposure, but this cannot be demonstrated in short-term studies only. On the other hand, as discussed earlier there are a several long-term studies showing associations in line with the ones presented in this thesis both for cardiac arrest and atrial fibrillation suggesting associations relevant in the long term and for an increased burden of cardiac arrhythmias related to ambient temperature and air pollution.

Second, our findings from these observational studies might be affected by residual confounding or misclassification. The case-crossover design will handle individual confounders that are stable over time well, but potential confounders related to meteorology or time-varying behaviors might confound the observed association. For Study III unmeasured factors related to time of day might confound the association as well.

The use of single monitors for exposure assessment in Study I, II and III will likely introduce some level of misclassification. We expect this misclassification to be non-differential and on average this should bias the result towards the null hypothesis or weaken the precision of the estimates. For Study II we used an ensemble model for exposure assessments that likely capture the personal exposure better than use of a single monitor. It comes with the drawback of potential introduction of a spatial misclassification with strong assumptions on the participants whereabouts. Personal monitors are not feasible for large retrospective studies and might come with its own trade-offs with potential personal behaviors related to air pollution exposure. These personal behaviors that are hard to measure could by themselves be related to health effects and therefore need to be controlled for (157).

It needs to be acknowledged that cardiac arrest is a heterogenous group and an end-stage for several different medical conditions. This might obscure potential relationships between environmental exposures and arrhythmias in the study setting of SRCR. In Study I and II we tried to make the group less heterogonous by only investigating cases with presumed cardiac (Study I) or medical (Study II) origin. In both Study I and II higher risks were observed in cases with a primary ECG rhythm of VT/VF. This patient population is more likely to have a cardiac arrest of cardiac origin and be a primary arrhythmic event. Stronger associations in this sub-population strengthens the hypothesis of a pro-arrhythmic effect of both cold ambient temperature and $PM_{2.5}$ exposure.

6 Conclusions

I. Ambient temperature below an optimum temperature was associated with increased risk of cardiac arrest in Stockholm. We observed positive associations for temperatures above the optimum temperature but they did not reach statistical significance. Results were consistent for both 24-h and 1-h mean ambient temperature exposure.

II. Short-term exposure to $PM_{2.5}$ and PM_{10} was associated with increased risk of cardiac arrest in Sweden. The results were robust for adjustment for temperature exposure. We did not find any susceptible subgroups.

III. PM_{10} exposure was significantly associated with the onset of acute episodes of both asymptomatic and symptomatic AF in a population of randomly selected 75-year-olds. We observed more pronounced associations for participants with hypertension, diabetes and overweight.

IV. Short-term increases in $PM_{2.5}$ in a low-pollution level environment were significantly associated with increased risk of AF episodes in a population with intracardiac devices. The associations were lagged with the most pronounced association for the 48–72-hours exposure window.

7 Points of perspective

Ambient environmental exposures such as ambient temperature and air pollution are affecting people globally and have a significant impact on public health. The findings from this thesis indicate that exposure to moderate changes from an optimum temperature and exposure to particulate matter at a low level increases the risk of cardiac arrhythmias. This has important implications as current estimations might underestimate the burden related to these exposures. Our findings also raise several questions and areas for potential further research. First, we observed associations for both temperature and air pollution separately. There is some evidence in the literature of a potential synergistic effects of co-exposure and this would be of great interest to investigate further, especially in the context of a changing climate with increased extreme weather events.

Second, the findings from this thesis need to be corroborated by studies investigating long-term exposure and disease burden. This is particularly important for air pollution exposure but also has a relevance for temperature.

Third, our findings of associations between PM exposure and arrhythmias below current regulatory standards and close to or below the new strict WHO guidelines raise questions from a regulatory standpoint. There is no evidence in previous literature of a clear threshold of a *safe* level of air pollution exposure but rather the opposite with suggestions of a superlinear exposure response curve with the greatest per increment risks at lower exposures. Given causal associations there would be health benefits from aiming for even lower air pollution levels then today's targets. Previous reduction from moderate to low levels in several high-income countries have most likely improved public health. However, reduction of air pollution levels from low to very low might not be feasible or at least come with high alternative costs. Some potential interventions might have co-beneficial effects on health, for example city planning with a reduction of cars in the cities and instead improved walkability, while other might have diverging effects with both benefits and increased risk for health. At any rate, interventions or regulations often comes with an economic cost that might or might not be overshadowed by the health benefit. I believe that this intricate balance with interventions, multiple exposures and alternative costs needs to be better understood and requires further studying.

Fourth, we did observe stronger risks in participants with diabetes and overweight. This could be of importance because of the increasing prevalence of obesity and the metabolic syndrome. We did not find any clear susceptible groups with regards to cardiac arrest. Future studies should further investigate potential groups at higher risks as this may be of importance for targeted interventions.

In summary, our results add to the evidence of an adverse effect of ambient temperature and particulate matter on cardiac arrhythmias, suggestive of harmful effects that need to be studied further.

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