Diplomarbeit

Cardiovascular Effects of Air Pollution: A Literature Review

eingereicht von

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unter der Anleitung von

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Graz, am 26.01.2020

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Graz, am 26.01.2020 *Agnes Maria Lederer eh.*

Acknowledgements

I would like to seize this opportunity to thank my supervisor Assoz. Prof. Priv.-Doz. Dr.med. Nandu Goswami PhD, who provided me with guidance and patient support throughout the entire process of writing my diploma thesis. His flexibility, and promptness in working with students and colleagues truly impressed me.
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Thank you, Philip, for being such a reliable partner and anchor in my life and for continuously challenging and inspiring me.

Zusammenfassung

Hintergrund: Luftverschmutzung ist ein weltweites Thema, welches in den letzten Jahren zunehmend an Bedeutung gewann. Immer mehr Nationen sehen sich mit den Folgen steigender Luftverschmutzung auf die Gesundheit sowie Gesundheitssysteme konfrontiert. Derzeit werden jährlich ca. 4.2 Millionen Todesfälle den erhöhten Konzentrationen an Luftverschmutzung zugeschrieben. Feinstaub, ein partikelförmiger Bestandteil von Luftverschmutzung, wurde kürzlich als eine der Hauptursachen für Mortalität und Morbidität weltweit eingestuft. Während die negativen Folgen auf das respiratorische System gut erforscht und bereits in der Öffentlichkeit bekannt sind, wurde der Einfluss von Luftverschmutzung auf das kardiovaskuläre System, bis vor kurzem, weniger berücksichtigt.

Ziele: Diese Diplomarbeit soll einen Überblick über die derzeit vorhandene Literatur zum Thema „Auswirkungen von Luftverschmutzung auf das kardiovaskuläre System“ geben. Ein besonderer Fokus wird dabei auf die Zusammenhänge zwischen Luftverschmutzung und dem Risiko für bestimmte kardiovaskuläre Erkrankungen gelegt. Weiters sollen potentielle Pathomechanismen, welche der gesundheitsgefährdenden Wirkung von Luftverschmutzung zugrundliegen, ermittelt werden.

Methoden: Es erfolgte eine systematische Durchsicht der derzeit verfügbaren Primär- sowie Sekundärliteratur. Pubmed, Web of Science und Google Scholar dienten als Suchmaschinen, um Zugriff zu medizinischen Datenbanken zu erhalten. Der Zugang zu benötigten Lehrbüchern wurde über die Bibliothek der Medizinischen Universität Graz gewährleistet. Weiters wurden aktuelle Informationen und Leitlinien der Weltgesundheitsorganisation, der Europäischen Umweltagentur sowie der American Heart Association für die Erstellung der Einleitung berücksichtigt. Forschungsergebnisse kürzlich veröffentlichter Studien wurden systematisch analysiert und verglichen.

Ergebnisse und Diskussion: Es wurden insgesamt 37 Publikationen als relevant befunden und in den Diskussionsabschnitt der Diplomarbeit integriert. Die Analyse der aktuellen Literatur zeigt deutliche Zusammenhänge zwischen Luftverschmutzung, hierbei vor allem Feinstaub, und dem jeweiligen Risiko für Blutdruckerhöhung, akutem Koronarsyndrom, Myokardinfarkt, Herzrhythmusstörungen und Herzinsuffizienz. Als mögliche, der schädlichen

Wirkung von Luftverschmutzung zugrundeliegenden, Pathomechanismen werden vor allem oxidativer Stress, systemische Entzündung sowie prothrombotische Prozesse und Störungen des autonomen Nervensystems diskutiert.
Schlussfolgerungen: Die Zusammenhänge zwischen Luftverschmutzung und kardiovaskulären Erkrankungen und Mortalität sind mittlerweile in der Literatur umfassend beschrieben. Bisherige Forschungsergebnisse zeigen, dass Luftverschmutzung ein globales Problem ist, welches die kardiovaskuläre Gesundheit von Individuen unterschiedlichen Alters, Geschlechts, Gesundheitszustands und Herkunft beeinflusst. Eine konsequente Umsetzung von Luftqualitätsrichtlinien hat in Zukunft möglicherweise das Potential, das Risiko für kardiovaskuläre Erkrankungen zu verringern.

Abstract

Background: Air pollution is an emerging global topic. More and more nations are confronted with the effects on health related to increasing levels of air pollution. Currently, 4.2 million deaths can be attributed to ambient air pollution each year. $PM_{2.5}$ ranks as one of the leading causes of disability and mortality. While the adverse effects of air pollution on the respiratory system are widely known, there has been less attention towards the impact of air pollution on the cardiovascular system.

Aims and objectives: This diploma thesis aims at providing an overview of the current literature regarding the effects of air pollution on the cardiovascular system. Special focus is placed on the relationship of air pollution and the risk of certain cardiovascular diseases. Additionally, mechanisms through which air pollutants interfere with the cardiovascular system are examined.

Methodology: An extensive review of the current literature, including primary and secondary sources of literature, was carried out. PubMed, Web of Science and Google Scholar served as search engines in order to access medical databases. Further access to textbooks was gained through the library of the Medical University of Graz. Additional information was obtained from webpages and guidelines of the WHO, the European Environmental Agency and the American Heart Association. Findings of recently published studies were systematically analyzed.

Results and discussion: A total of 37 publications was finally identified as relevant and included in the discussion. Analysis of the current literature showed significant associations between air pollution, especially of $PM_{2.5}$, and the risk of elevated blood pressure, acute coronary syndrome, myocardial infarction, cardiac arrhythmia and heart failure, respectively. Potential mechanisms that underlie the adverse effects of air pollution include oxidative stress, systemic inflammation, autonomic imbalance and thrombogenicity.

Conclusions: Associations between exposure to air pollution and cardiovascular morbidity and mortality have been well documented. The collected evidence of this review suggests that air pollution is a global issue affecting the cardiovascular health of individuals of different age groups, sex, health status and ethnicity. In the future, rigorous implementations of air quality guidelines may have beneficial effects on the risk of developing cardiovascular diseases.

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Glossary and Abbreviations

8- epi-PGF2a	8-epi-prostaglandin F2a
AAC	abdominal aortic calcification
AAP	ambient air pollution
ABI	ankle-brachial index
ACC	American College of Cardiology
ACS	acute coronary syndrome
ADHF	acute decompensated heart failure
AF	atrial fibrillation
AHA	American Heart Association
AMI	acute myocardial infarction
ANS	autonomic nervous system
BC	black carbon
BNP	brain natriuretic peptide
BP	blood pressure (mmHg)
BTEX	benzene, toluene, ethyl-benzene, m+p-, o-xylenes
CAC	coronary artery calcification
CAD	coronary artery disease
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CIMT	carotid intima-media thickness
CRP	C-reactive protein
CVD	cardiovascular disease
CVS	cardiovascular system
DBP	diastolic blood pressure (mmHg)
ECG	electrocardiogram
eNOS	endothelial-derived nitric oxide synthase
ERVs	emergency room visits
ESCAPE	European Study of Cohorts for Air Pollution Effects
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio

HRV	heart rate variability
HT	hypertension
IHD	ischemic heart disease
IL-6	interleukin-6
IMT	intima-media thickness
IQR	interquartile range
IRR	incidence rate ratio
LV	left ventricle
LVEF	left ventricular ejection fraction
MI	myocardial infarction
NE	norepinephrine
NO	nitric oxide
NSTE ACS	non–ST elevation acute coronary syndrome
NSTEMI	ST-elevation myocardial infraction
NT-BNP	n-terminal pro-brain natriuretic peptide
OR	odds ratio
PM	particulate matter
PNS	parasympathetic nervous system
PP	pulse pressure
ppb	parts per billion
ppm	parts per million
RAAS	renin-angiotensin-aldosterone system
ROS	reactive oxygen species
RR	risk ratio or relative risk
SBP	systolic blood pressure (mmHg)
SNS	sympathetic nervous system
STEMI	ST-elevation myocardial infarction
TAA-PNC	time-activity-adjusted particle number concentrations
TAC	thoracic aortic calcification
TRAP	traffic-related air pollution
UA	unstable angina
UFPs	ultrafine particles
WHO	World Health Organization

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1 Introduction:

1.1 Air Pollution

1.1.1 Pollutants

Air pollution is a broad term which does not refer to one single pollutant, but rather to a complex and varying conglomerate of numerous air pollution components. Particulate matter (PM), nitrogen oxides (NO_x), carbon monoxide (CO), ozone (O_3) and sulfur dioxide (SO_2) are considered the main air pollutants (1). PM consists of liquid and solid particles that exist as a suspension in the air. Since the particles originate from different sources, they vary greatly in chemical composition and size (2,3). Some of the components commonly found in particulate air pollution are sulphates, nitrates, black carbon (BC), endotoxin, various metals, mineral dust and water (1,4).

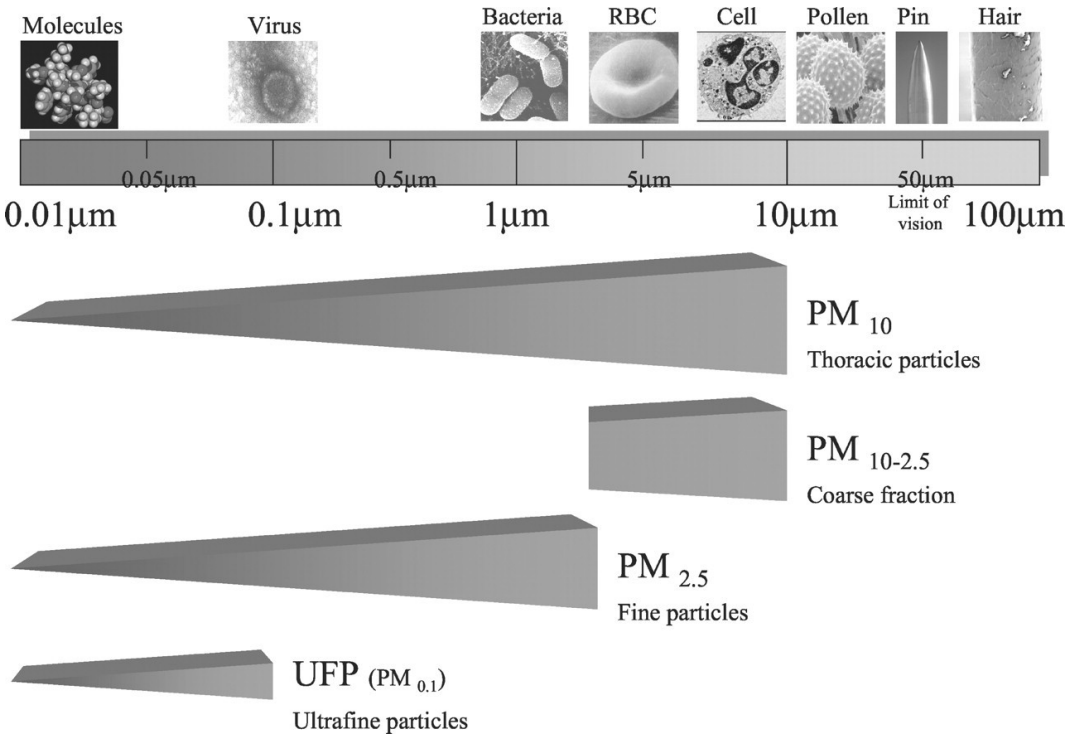

Figure 1: Particulate air pollution: particle sizes
(reproduced from: (4))

Based on the size of the particles a classification into three major groups can be made: coarse particles (diameter 2,5-10 µm), fine particles (< 2,5 µm) and ultrafine particles (UFPs; < 0,1 µm) (4). In practical terms, the abbreviation PM_{10} is used to

describe particles with a diameter less than 10 µm. $PM_{2.5}$, accordingly, refers to the fine fraction of particulate matter (3).
$PM_{2,5}$ accounts for up to 70% of the total mass of PM_{10}, whereas UFPs hardly contribute to the mass of particulate air pollution, but dominate in terms of numbers (5).
Nitrogen oxides (NO_x) is a collective term referring to nitrogen monoxide (NO) and nitrogen dioxide (NO_2). While NO accounts for a large proportion of total NO_x emissions, NO_2 is considered more harmful to human health (2).
Ground-level ozone is a characteristic component of photochemical smog. It is a particularly relevant greenhouse gas contributing to global warming. Due to its reactive nature, it is one of the most aggressive components of gaseous air pollution (1,2).
SO_2 mainly originates from power plants and burning of oil and coal. SO_2 reacts with water in the air which subsequently leads to acid rain. Its adverse effects on health mostly comprise symptoms and diseases of the respiratory system (6).
CO is mainly produced from motorized traffic and combustion of fossil fuels. Outdoor CO concentrations are particularly high in developing countries. At higher levels, CO leads to impairment of oxygen transportation, which can acutely manifest as symptoms like nausea, headache, confusion, angina and syncope. Long-term exposure to lower levels of CO can lead to a variety of health problems primarily involving the cardiovascular, respiratory and nervous system (1,7).

1.1.2 Sources of Air Pollution

Based on occurrence and distribution, a distinction between indoor and outdoor air pollution can be made. Indoor pollutants mainly originate from residential use of harmful biomass fuels for heating, cooking and lighting. Due to meteorological circumstances (temperature, wind, sun) and ventilation patterns, the concentrations of outdoor pollutants change and often differ of those inside households. The sources of outdoor pollution are primarily man-made or anthropogenic and include combustion of fossil fuels in transport, industry, electricity generation, waste-material processing and the agricultural sector. Natural sources comprising volcanos, forest fires, windblown dust and organic compounds from plants also contribute to outdoor air pollution, but their impact is considerably smaller (2,3,8). Depending on the origin, a further classification into

primary and secondary pollutants is common. Fires, unpaved roads and burning of fossil fuels lead to direct emission of pollutants, mainly NO_2 and SO_2 and PM, into the atmosphere (primary emissions). Secondary emissions (ozone, PM) originate from traffic, power generation and industrial procedures and are not directly emitted into the atmosphere, but formed by complex chemical reactions involving precursor pollution components such as NO_x and CO (3,5,8).

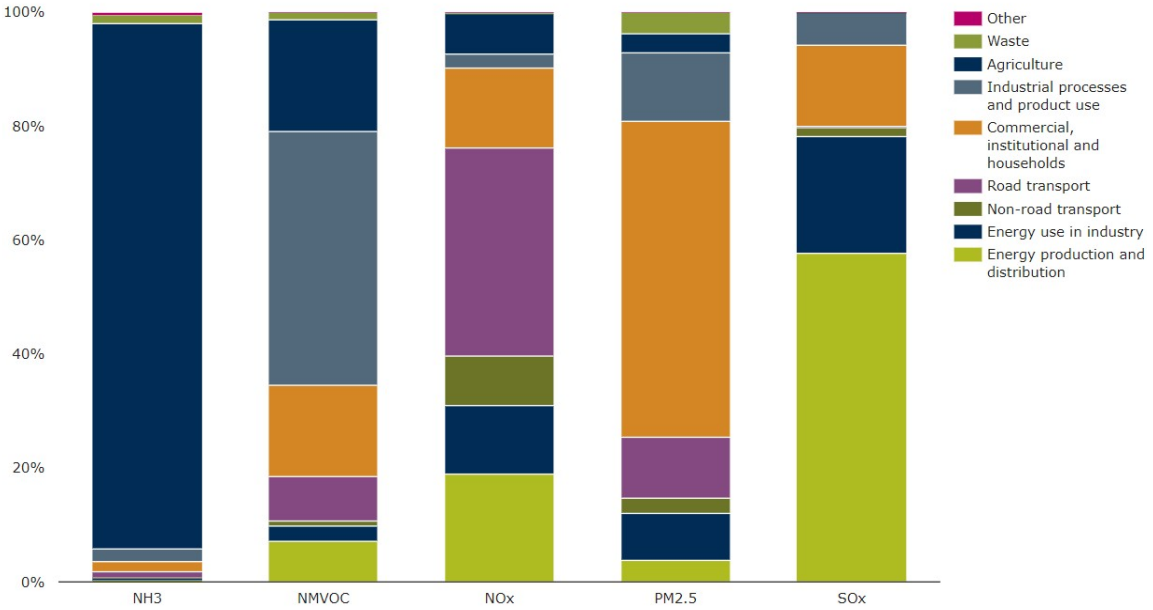

Figure 2: Emissions by sector group
(reproduced from: https://www.eea.europa.eu/data-and-maps/indicators/main-anthropogenic-air-pollutant-emissions/assessment-6, Access 14.11.2019)

$PM_{2.5}$ consists of primary and secondary particles. Like UFPs, it is mainly a product of combustion processes. Coarse particles, on the other hand, primarily originate from natural sources and often contain bioaerosols, like endotoxin, fungal spores and pollen grains (4).

In comparison, NO_2 is typically associated with motorized traffic. Other sources of NO_x are power plants and industrial facilities (1).

1.1.3 Air Quality: Guidelines and Global Perspectives

Historic events have shown impressively that air pollution can be life-shortening. Perhaps the most well-known of those incidents in the past is the “Great smog of London” in 1952, in which the death rate rapidly tripled in London due to unfortunate weather and wind conditions that caused severe smog formation and immensely increased levels of air pollutants. Not only acute impact of air pollution

on mortality, but also long-term effects on human health were observed at that time (9).

With the aim of protecting human health, different regulations regarding air quality have been established in the last decades.

Following pollutant concentration levels are recommended in the current air quality guidelines of the WHO (10):

- annual mean $PM_{2.5}$ concentrations: < 10 µg/m^3, 24-h mean: < 25 µg/m^3
- annual mean PM_{10} concentrations < 20 µg/m^3, 24-h mean: < 50 µg/m^3
- 8-h mean O_3 concentrations < 100 µg/m^3
- annual NO_2 concentrations: < 40 µg/m3, 1-h mean: < 200 µg/m^3
- 24-h mean SO_2 concentrations: < 20 µg/m^3, 10-minute mean: <500 µg/m^3

EU target values are less stringent and were set at (11):

- annual $PM_{2.5}$ concentrations: 25 µg/m^3
- daily PM_{10} concentrations: 50 µg/m^3 for more than 35 days/year
- daily 8-hour mean O_3 concentrations: 120 µg/m^3 for more than 25 days/year
- annual NO_2 concentrations: 40 µg/m^3

Because of these policies and additional innovations, air quality in Europe has improved in recent decades. Nevertheless, monitoring at traffic and background stations in Europe still demonstrated considerable exceedances of the EU and WHO thresholds for NO_2, PM_{10} and $PM_{2.5}$ in 2016 (12).

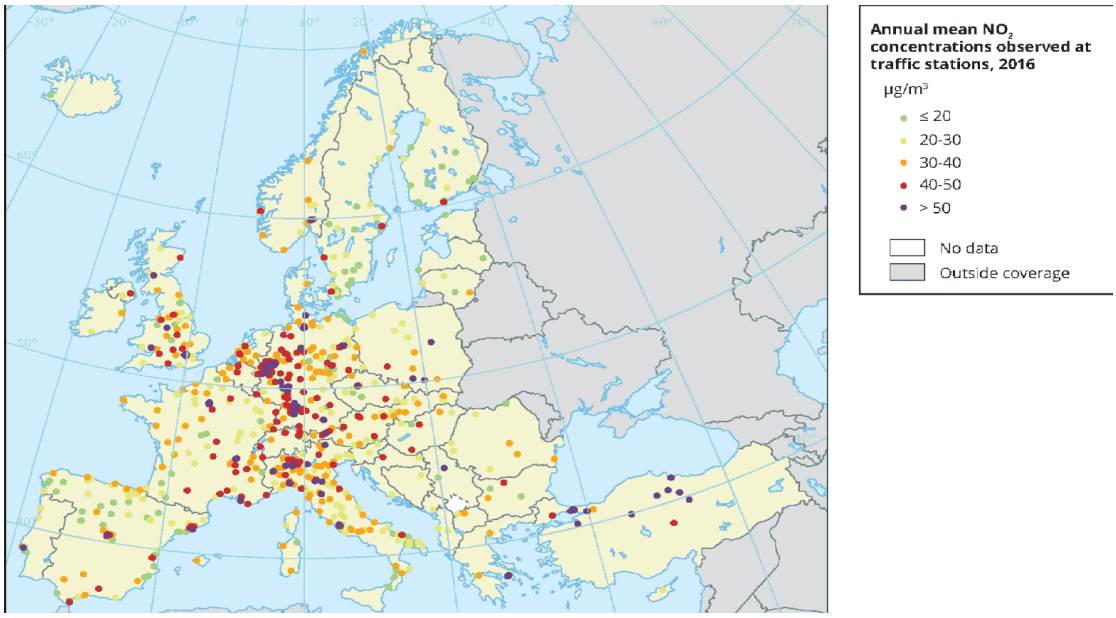

Figure 3: Mean concentration levels of NO_2 at European traffic stations in 2016
(reproduced from: https://www.eea.europa.eu/data-and-maps/figures/annual-mean-no2-concentration-observed-11, Access 17.11.2019)

As depicted in Figure 4, a considerable number of individuals residing in European cities are still exposed to pollution concentrations that exceed EU and WHO air quality guidelines (11).

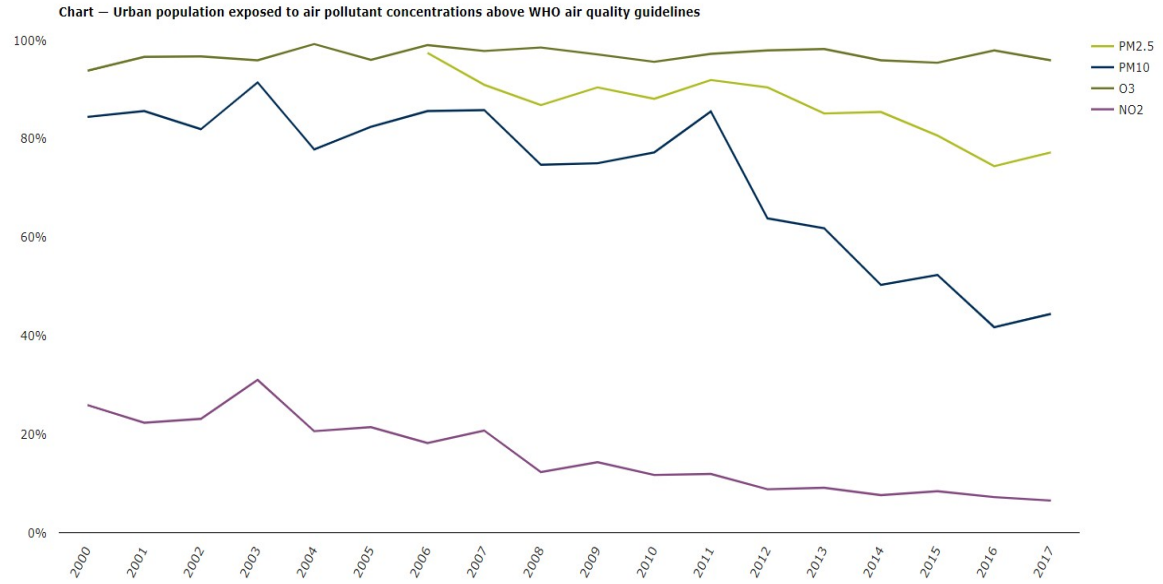

Figure 4: Percentage of European urban population exposed to pollution concentrations above WHO air quality guidelines
(reproduced from: https://www.eea.europa.eu/data-and-maps/indicators/exceedance-of-air-quality-limit-3/assessment-5, Access 16.11.2019)

From a global perspective, low- and middle-income countries, especially some regions in Western Pacific and South-East Asia, are most affected by air pollution (13). People who live in developing countries and rural areas are particularly at

risk of being affected by air pollution, since the use of coal for domestic heating and cooking is still common in those regions (14).
Compared to other continents, only a few studies that investigated the health effects of air pollution have been carried out in Africa. Due to a lack of adequate environmental monitoring, there is hardly any useable data regarding exposure to ambient air pollution (AAP) in sub-Saharan regions and Africa in general. Since the majority of research was based on a cross-sectional study design and often relied on self-report questionnaires, it is difficult to reliably estimate the long-term outcomes associated with exposure to air pollution in Africa. Moreover, the shortage of sufficient data material is particularly problematic because in many African cities exposure levels are presumably higher than the current WHO recommendations and are expected to further increase due to growing cities and populations (15).

1.1.4 Health Impacts

AAP is an increasingly recognized health concern worldwide. Exposure to air pollution has been linked to increased rates of hospitalization and emergency room visits (ERVs) (16). According to the WHO, around 4.2 million deaths per year are attributable to AAP. Cardiac diseases, stroke, pulmonary cancer and chronic pulmonary diseases account for the vast majority of these deaths (13). Furthermore, it is estimated that AAP attributes to 25% of all deaths and disease from ischemic heart disease (IHD) and even more than 40% of all deaths and disease from COPD, globally (16). Individuals with short- and long-term exposure to air pollution are more susceptible to respiratory infections and development of asthma. Additionally, other health outcomes, such as low birth weight and premature birth have been shown to be associated with exposure to AAP during pregnancy.

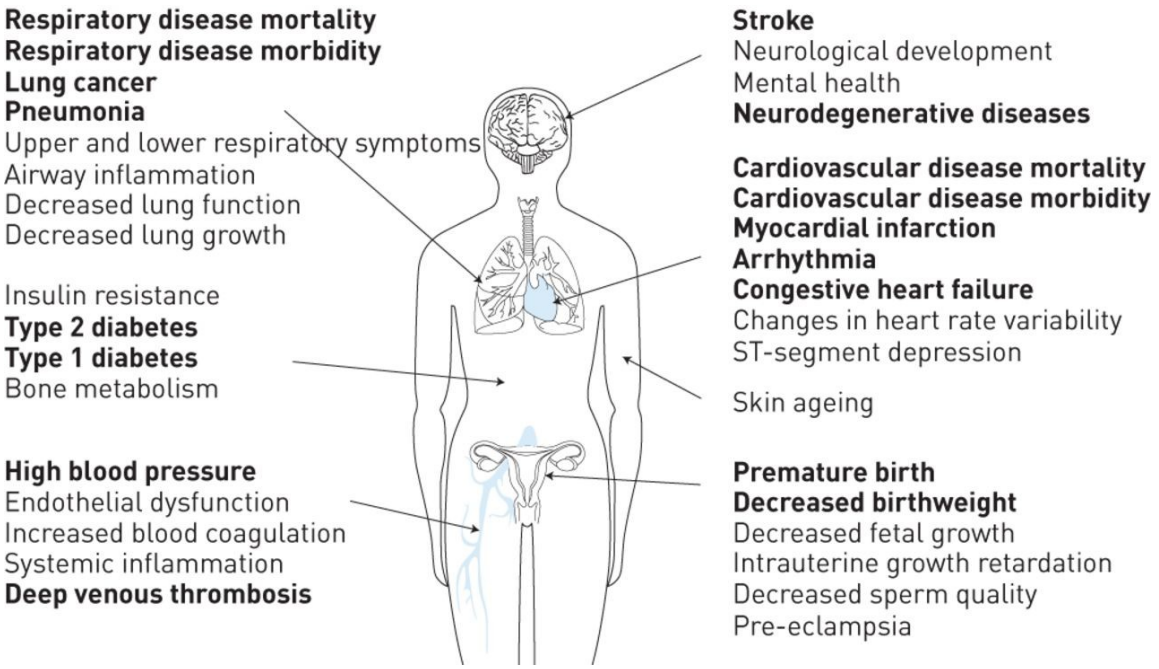

Figure 5: Adverse health effects of air pollution
(reproduced from: (17))

Among all air pollutants, PM, NO_2, ozone and SO_2 are considered the most harmful to human health. Evidence suggests that PM_{10} and $PM_{2.5}$ have particularly strong adverse effects on the CVS and heath in general (16). According to a recent assessment regarding global burden of disease, $PM_{2.5}$ now ranks as one of the leading causes of death and disability (18). The variations in particle size and composition result in different degrees of toxicity (3). Depending on the size fraction, PM can act at various sites and levels in the human body, which, in turn, explains the broad spectrum of its negative health effects. PM_{10} is referred to as “thoracic particles” due to the fact that they accumulate mostly in the upper airways and can penetrate into the lower respiratory tract (4). Fine particles, on the other hand, are called “respirable particles” and reach the alveolar regions of the lungs. Facilitated by their small size and large surface area, UFPs can most easily penetrate deeper into the lungs and even enter the bloodstream, which can then lead to direct systemic effects (3,14,16). PM is often used as a surrogate parameter when determining the overall health impact of AAP (16). Experience has shown that there is often a dose-dependent correlation between health outcomes and certain levels of pollutant concentrations. These concentration-response functions are therefore commonly used in the risk estimations of air pollution (19).

More and more evidence suggests that other air pollutants, like NO_2 and O_3, are independent risk factors for respiratory illnesses like asthma and bronchitis and also contribute to cardiovascular morbidity and mortality (1,2).

1.2 Cardiovascular Disease

1.2.1 General Aspects and Global Burden of Disease

Within the CVS a great variety of problems or pathologies may occur. Among these cardiovascular issues, certain conditions that affect the blood vessels or the heart are referred to as cardiovascular diseases (CVDs). CVDs typically comprise coronary artery disease (CAD) or coronary heart disease (CHD), myocardial infarction (MI), cerebrovascular disease, peripheral arterial disease, thrombosis or embolism, rheumatic heart disease and congenital heart disease (20). According to the WHO, CVD is a major global health topic. CVD is the leading cause of death worldwide. An estimated 17.9 million deaths were attributed to CVDs, which corresponds to 31% of all deaths in the year of 2016 (21).

1.2.2 Blood Pressure and Arterial Hypertension

Arterial hypertension is the single most potent driving factor behind cardiovascular morbidity and mortality. In 2015, 10.7 million deaths and almost 212 million disability-adjusted life years were attributable to elevated systolic blood pressure (SBP), worldwide. While in 1975 the number of grown-ups with hypertension was 594 million, the amount of affected people almost doubled in the subsequent 40 years (22). At present, the prevalence is estimated 30-45% of the general population in European countries (23).

Given that hypertension is a preventable cardiovascular risk factor, it is of major importance to comprehend the mechanisms and influences linked to the development of arterial hypertension.

1.2.2.1 General Aspects

Blood pressure (BP) generally describes the pressure in large arteries in the systemic circulation. Hence, it is commonly referred to as systemic arterial pressure (24). The arterial blood pressure reaches its maximum when blood is pumped from the heart into the aorta during systole. It is therefore referred to as systolic blood pressure. Diastolic blood pressure (DBP), in turn, is the minimum

BP within the large arteries that occurs at the end of the ventricular relaxation (diastole) (25). Arterial pressure needs to be precisely regulated, in order to contiunally ensure perfusion of tissue and organs (24).

1.2.2.2 Blood Pressure Regulation and Development of Arterial Hypertension

A variety of mechanisms is involved in the regulation of BP (24). Since cardiac output and peripheral vascular resistance basically determine arterial blood pressure, all BP-regulating pathways are ultimately leading to a change in either of those two variables. The renin-angiotensin-aldosterone system (RAAS) controls BP through regulation of blood volume (angiotensin II, aldosterone) and peripheral vascular resistance (angiotensin II). Besides RAAS, the autonomic nervous system (ANS) is vital component of BP regulation (25).

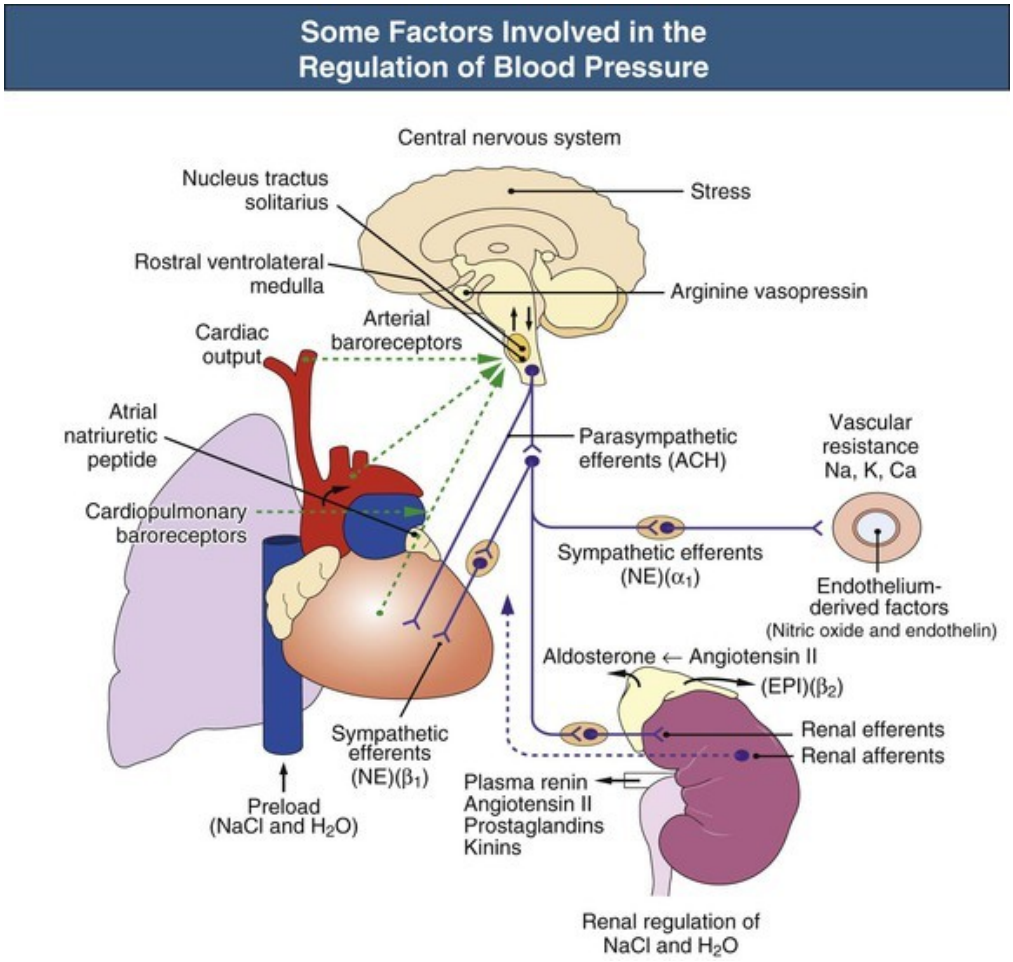

Figure 6: Regulation of blood pressure
(reproduced from: https://abdominalkey.com/normal-blood-pressure-control-and-the-evaluation-of-hypertension/, Access 06.11.2019)

1.2.2.2.1 Autonomic Nervous System and Autonomic Dysfunction

The ANS, consisting of a sympathetic (SNS) and parasympathetic (PNS) division, is the most important regulator of BP. The effects of sympathetic efferents and norepinephrine (NE), as the humoral component of the SNS, are mostly mediated by α1, β1 and β2 receptors. Activation of the SNS increases cardiac inotropy, chronotropy and dromotropy and triggers α1-receptor-mediated vasoconstriction, which, together, leads to BP elevation. The PNS, on the other hand, has counteracting effects on BP. Through vagal control of the heart it is involved in lowering of BP (25). Not surprisingly, a dysfunction of the autonomic cardiovascular control is therefore closely linked to the origin and progression of hypertension. Hyperactivity of the sympathetic division, but also impairment of vagal cardiac regulation, can both contribute to the development of hypertension. The sympathetic overdrive and adrenergic activation result in abnormal increases in circulating catecholamines and in an excessive stress response to environmental stimuli. Additionally, a decreased parasympathetic influence on the heart may simultaneously contribute to a hypertensive state. Those vagal abnormalities are linked to reduced heart rate variability (HRV) as measured by fluctuations of the R-R interval (26). HRV, therefore, indicates an imbalance of the ANS and is frequently used to assess autonomic dysfunction (27).

1.2.2.2.2 Baroreceptor Reflex

Acute changes in BP leads to activation of baroreceptors. High-pressure baroreceptors are mainly located at the carotid sinus as well as in the aortic arch. Stretching and distortion of the vascular wall act as mechanic stimuli and cause an activation of baroreceptors. The signal is then transmitted to the brain as well as to the ANS which initiates subsequent processes with the aim of normalizing BP. Low-pressure baroreceptors, on the other hand, are found in large veins, the right atrium and ventricle and in pulmonary vessels. They are primarily sensitive to changes in blood volume and cardiac preload and are closely linked to RAAS (24). Due to cell damage and stiffening of the vessel wall, the ability of baroreceptors to respond to changes in BP is reduced, which in turn has prohypertensive effects (26).

1.2.2.2.3 Endothelial (Dys-) Function

As the innermost layer of the blood vessel wall, the endothelium is involved in BP regulation. The endothelium plays a crucial role in production and release of vasoconstricting and vasodilating agents, thus, it modifies blood flow on a local level. Nitric oxide (NO) is considered the most relevant vasodilator. It is synthesized by endothelial-derived nitric oxide synthase (eNOS) and released by endothelial cells into the blood stream where it sets off a cascade resulting in relaxation of the blood vessel (25). The synthesis and release of NO is triggered by several factors such as shear stress and mechanic strain, thrombin, serotonin, adenosine diphosphate (ADP), acetylcholine and bradykinin (28). The most potent vasoconstrictor, on the other hand, is endothelin-1, followed by angiotensin II, reactive oxygen species (ROS), prostaglandin H_2 and thromboxane A_2 (25).
Damage to the endothelium, caused by CV risk factors, results in endothelial dysfunction. Typically, endothelium-mediated vasodilation is impaired in the presence of endothelial dysfunction. It occurs due to reduced production and availability of vasodilating factors, primarily NO, and simultaneous predominance of endothelium-derived vasoconstrictors. Additionally, endothelial dysfunction also refers to an activated proinflammatory, pro-coagulatory and proliferative state of the endothelium. These chronic inflammatory processes of the endothelium are linked with formation of oxidative stress (ROS), which in turn, favors further endothelial injury and cell death.
Finally, impairment of endothelial function was directly linked to the development of atherosclerosis and plays a key role in plaque progression. Endothelial dysfunction can, therefore, be considered a separate factor in the pathophysiology of several CVDs (29).

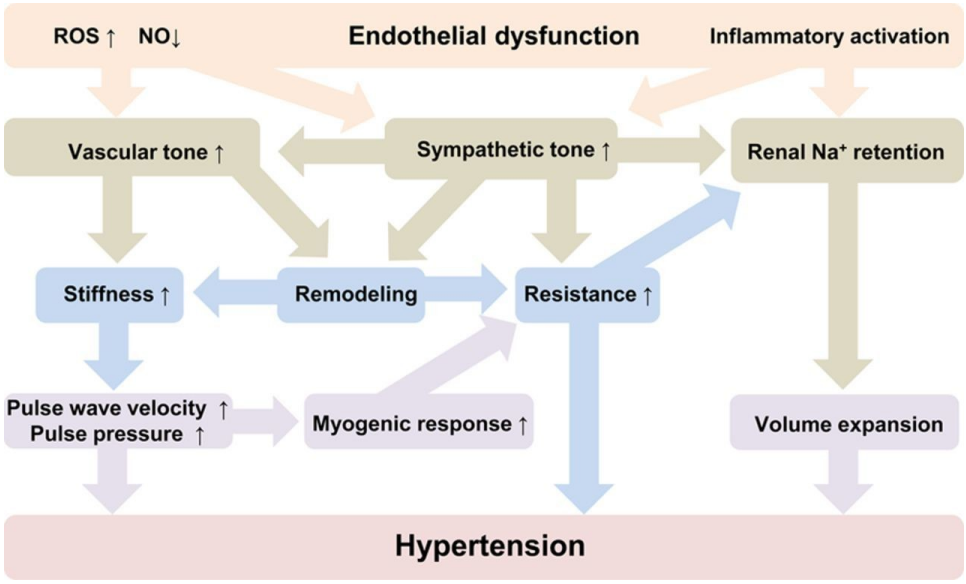

Figure 7: Pathways from endothelial dysfunction to hypertension (reproduced from (30))

1.2.2.3 Arterial Hypertension

The classification of hypertension was modified in recent years. The new classification of the American College of Cardiology (ACC) and the American Heart Association (AHA) categorizes BP into: normal, elevated, stage 1 and stage 2 hypertension and hypertensive crisis (see Figure 5) (31). Resting average BP levels < 115/75 mmHg are considered optimal (32). Structural and functional vascular changes and exaggerated responses to exercise or stress, are early signs of the hypertensive disease that may already be detectable at the stage of "elevated blood pressure" (33). In terms of BP levels, individuals of stage 1 typically have BP levels between 130 and 139 mmHg. With progression to stage 2 sustained resting BP levels ≥140/90 mmHg can be observed. A hypertensive crisis is characterized by SBP levels >180 mmHg and/or DBP >120 mmHg (31). Essential hypertension is the most common form of arterial hypertension. Obesity, excessive alcohol consumption, smoking, genetic predisposition, salt sensitivity, chronic stress and a sedentary lifestyle are the most relevant risk factors and share a causal co-responsibility in the pathogenesis of essential hypertension (25,34) Generally, those CV risk factors influence BP through the above mentioned mechanisms, including activation of the SNS, endothelial dysfunction, suppression of the natriuretic peptide system and hyperactivation of RAAS (31).

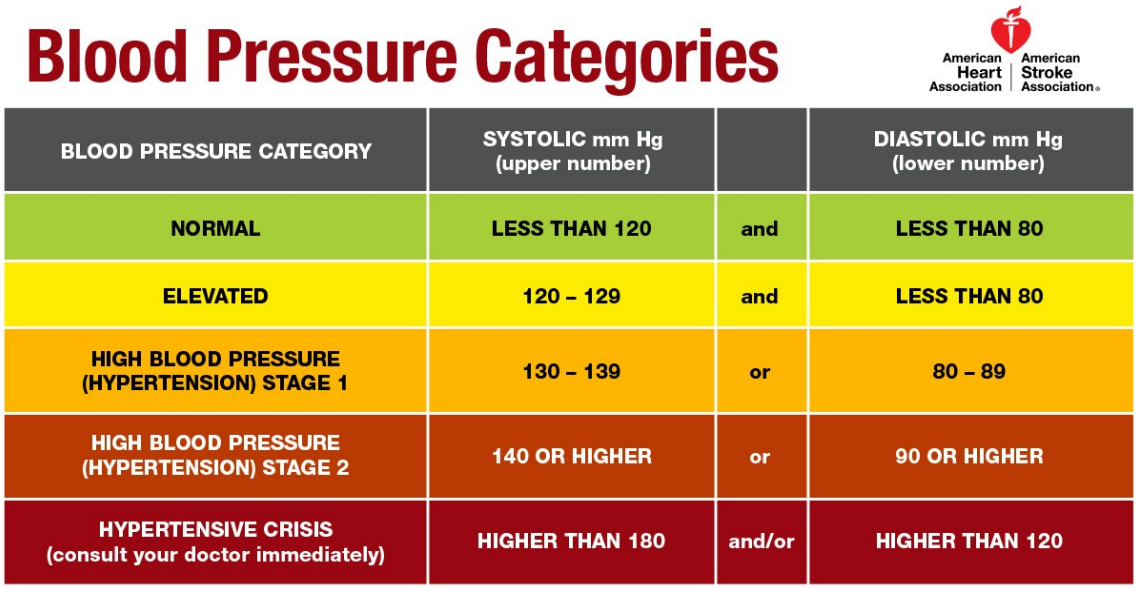

Figure 8: Blood pressure categories
(reproduced from: https://www.medpagetoday.com/meetingcoverage/aha/69247, Access 12.11.2019)

Demonstrated by steep increases in prevalence with ageing, age has a particularly strong impact on the risk of developing hypertension (23).

Over time, hypertension leads to structural changes in blood vessels (atherosclerosis) and injury of various organ systems (end organ damage). The most common consequences of hypertension for the heart itself comprise left ventricular hypertrophy, diastolic dysfunction, cardiac arrhythmias including atrial fibrillation (AF), congestive heart failure (CHF) and coronary insufficiency. Hypertension also impairs renal circulation, leading to nephrosclerosis and renal failure. In the large- and medium-sized arteries (macroangiopathy) it accelerates the formation of atherosclerosis and aneurysms. It is also associated with ischemia, hemorrhagic and thrombotic infarction in the brain, erectile dysfunction and retinopathy (23,25,35).

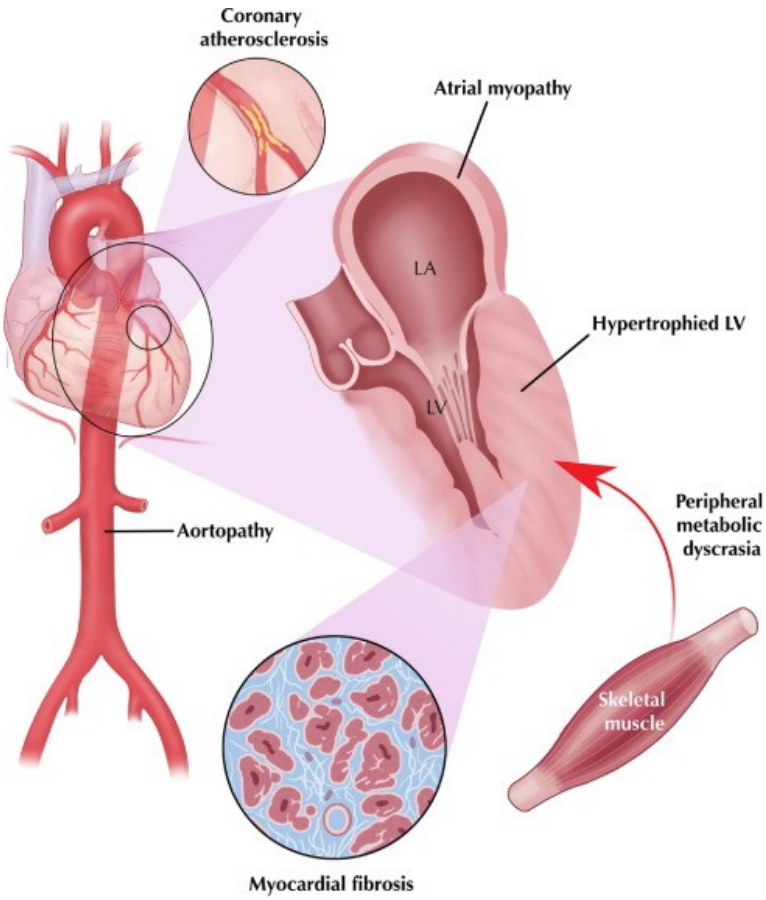

Figure 9: Aspects of hypertensive heart disease
(reproduced from: (36))

1.2.3 Hemostasis and Thrombosis

The term “hemostasis”, which literally translated means “blood stopping”, sums up multiple events that take place physiologically every time a blood vessel is injured. Its purpose is to prevent excessive blood loss. It is therefore a crucial mechanism in securing survival. The process leading to hemostasis, at the end of which a blood clot is formed, is a very complex one and, therefore, will only be discussed here in a simplified manner. Following four phases can be distinguished (37,38):

- Arteriolar vasoconstriction is the immediate response to vascular injury. It is initiated by autonomous neurogenic reflexes as well as by the endothelium itself, which releases an extremely potent vasoconstrictor: endothelin. Vasoconstriction leads to local reduction of blood flow which transiently stops the bleeding.
- The next phase is called primary hemostasis and results in formation of a primary hemostatic plug. It involves adhesion, activation, aggregation and further recruitment of platelets, which is mediated by von Willebrand Factor, secretory granules and collagen.

- It is followed by secondary hemostasis which purpose is the consolidation of the initial platelet plug. This is accomplished by a cascade of events: coagulation factors, release of tissue factor, activation of factor VII, generation of thrombin and finally the cleavage of fibrinogen into fibrin by thrombin. Fibrin, with its adhesive effects, leads to further stabilization and growth of the platelet plug.
- In the last phase, the thrombus formation is completed by contracting platelets and fibrin into a firm permanent plug. Concurrently, certain processes that lead to disintegration of the thrombus (fibrinolysis) are already initiated (37,38).

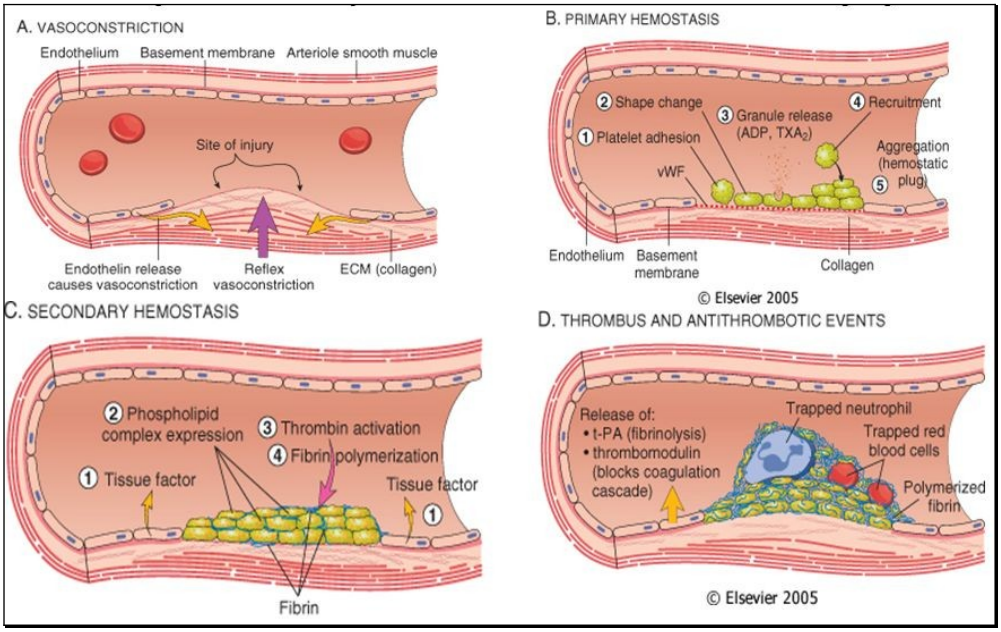

Figure 10: Hemostasis and thrombosis
(reproduced from (37))

Thrombosis, on the other hand, is defined as the pathological formation of a clot. The composition of this abnormal clot (thrombus) as well as the underlying prothrombotic triggers depend on the site of its origin, vein or artery. Venous thrombosis predominantly occurs in the deep veins of the legs, as deep vein thrombosis, or in the form of pulmonary embolism, whereas platelet-rich arterial clots are mostly located in the coronary arteries and play a role in MI.
There are three main factors, known as the Virchow triad, that contribute to thrombogenesis: endothelial injury, blood flow disturbances and hypercoagulability of the blood (37,38).

1. Endothelial injury, on the one hand, directly promotes thrombosis by activation of platelets. On the other hand, the endothelium itself can be in a prothrombotic state. This prothrombotic state, called endothelial dysfunction, is a result of proinflammatory cytokines, hypercholesterinemia, infection (bacterial toxins) and other toxic agents (i.e. cigarette smoke). These risk factors cause an activation of endothelial cells, which in turn leads to inhibition of antithrombotic and fibrinolytic genes (37).
2. Changes in blood flow occur either in the form of stasis or turbulence. Turbulences most frequently develop when blood vessels are narrowed, which is the case in sites of atherosclerosis and ruptured plaques (39). Hence, turbulences are associated with the development of arterial thrombosis. Stasis, on the other hand, can be caused by aneurysms, atrial fibrillation, hyperviscosity of the blood or immobility of the patient, all of which diminish blood flow. It mostly results in venous thrombosis. Generally, altered blood flow promotes thrombus formation by increasing the contact between thrombocytes and endothelial cells, enhancing platelet adhesion, activating the endothelium and by directly causing endothelial injury (37).
3. In hypercoagulable conditions, the properties of the blood itself are changed. Thus, the balance is shifted towards a more procoagulant state. Depending on the underlying cause, it is usual to differentiate primary or inherited hypercoagulability (i.e. APC-resistance, Protein C and Protein S deficiency, hyperprothrombinemia) from secondary or acquired hypercoagulability (malignancies, oral contraceptives, smoking etc.) (37).

1.2.4 Ischemic Heart Disease

The term “ischemic heart disease” covers a broad spectrum of pathologic conditions that are marked by an inadequate blood supply to the cardiac muscle cells, resulting in ischemia of the myocardium (40).
IHD is often used synonymously with the term “coronary heart disease” or “coronary artery disease” due to the fact that, in > 90% of cases, the underlying pathology involves an impaired blood flow in the coronary vessels, with atherosclerosis being the principal cause of reduced blood supply (37).

The development of atherosclerosis is a chronic process, which is known to have its origin already in childhood and adolescence. CAD progresses over decades. Its clinical manifestations are usually observed later in adulthood (41). When atherosclerotic plaques grow larger, they finally protrude into the lumen of the vessels. There, they might lead to either partial or total obstruction through following acute or chronic processes:

Acute rupture of an atherosclerotic plaque: It is the most frequent reason for acute coronary syndrome (ACS) such as unstable angina (UA) and acute myocardial infarction (AMI) (37).

Formation of a thrombus due to endothelial damage and direct contact of blood cells with the plaque: The clot can either cause local vascular occlusion or it may detach and be carried away into a more distal section of the artery where it may lead to acute blockage, called coronary embolism.

Another cause of myocardial ischemia is coronary artery spasm. Here again, an atherosclerotic plaque may be the triggering factor by irritating the vessel wall, subsequently leading to spastic contractions of the smooth muscles. Additionally, the spasm can be a result of reflexes, controlled by the nervous system which innervates the smooth muscle cells of the arterial wall. Blood flow alterations due to spasms may in turn promote clot formation (39).

Furthermore, CHD can be divided into three subgroups:

obstructive and nonobstructive CHD and coronary microvascular disease. The former two are associated with a reduced blood flow in the major coronary arteries (epicardial coronary arteries) and often occur together, whereas the latter affects finely branched arteries located deeper within the myocardium (subendocardial/intramural arteries). The degree of vessel occlusion distinguishes the nonobstructive form of CHD from the obstructive one (42).

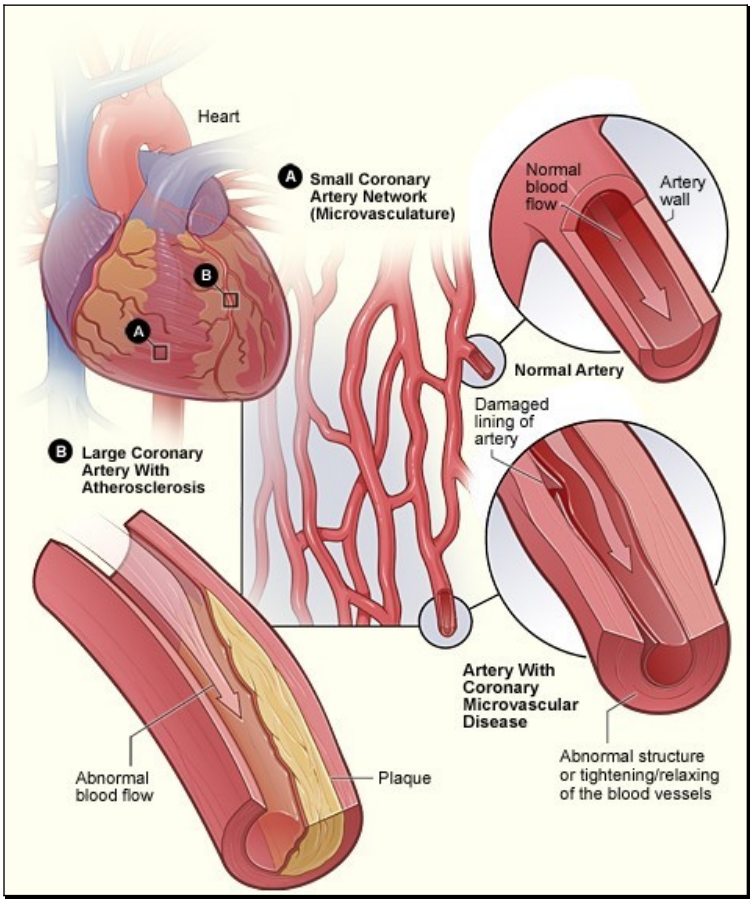

Figure 11: Coronary microvascular disease and coronary artery disease in large arteries (reproduced from: (42))

1.2.5 Acute Coronary Syndrome and Myocardial Infarction

In its most severe and fatal form, IHD presents as acute myocardial infarction. MI is defined as necrosis of cardiac muscle cells on the basis of a prolonged deprivation of oxygen. In around 90% of cases, the reason for this insufficient oxygen supply is acute coronary thrombosis, caused by an abruptly ruptured atherosclerotic plaque. This results in a sudden occlusion of a - usually epicardial - coronary artery followed by the death of cardiac cells in the area of supply of that blocked artery (43). Since AMI is strongly related to atherosclerosis, it shares the same risk factors, such as arterial hypertension, smoking, diabetes, dyslipidemia and hereditary factors. Additionally, older people, men and patients with a history of CAD or renal insufficiency have a increased risk of AMI (44,45).
AMI is a form of acute coronary syndrome. ACS is a collecting term referring to different degrees of acute myocardial ischemia. Based on certain clinical aspects it is possible to categorize ACS further into:

- ST-elevation ACS or ST-elevation myocardial infarction (STEMI) which typically presents itself as elevation of the ST-segment in the ECG persisting for at least 20 minutes, common symptoms, such as chest or arm pain, and characteristically high blood levels of troponins. STEMI is associated with a large infarct area, due to complete occlusion of a coronary artery. ST-elevations as well as troponin-levels correlate with the degree of transmural myocardial ischemia (45,46).
- non–ST elevation (NSTE) ACS shows no elevated ST-segment in the ECG. NSTE ACS can clinically manifest as either ST-elevation myocardial infraction (NSTEMI) or as unstable angina (UA). Through cardiac biomarkers in the blood, it is possible to differentiate the former (elevated troponins) from the latter (normal troponin-levels). NSTE ACS is usually associated with a non-occlusive thrombus. However, the underlying causes of NSTEMI appear to be much more diverse than that of STEMI. While the pathophysiology of STEMI generally involves the aforementioned, sequential series of atherosclerotic plaques, plaque rupture, thrombosis and total blockage of a coronary artery, the broad spectrum of conditions triggering NSTEMI ranches from stable plaques, coronary embolism, vascular spasm to arteritis and myocarditis. Also, many other factors that aggravate the mismatch between oxygen demand and supply may induce NSTEMI. These include BP alterations, tachycardia, pulmonary embolism and stenosis of the aortic valve.

  Patients with NSTEMI may present very similar to those diagnosed with UA. Although this form of AMI is usually considered less severe, its clinical manifestation can ranch from absence of symptoms to cardiac arrest (45,46).

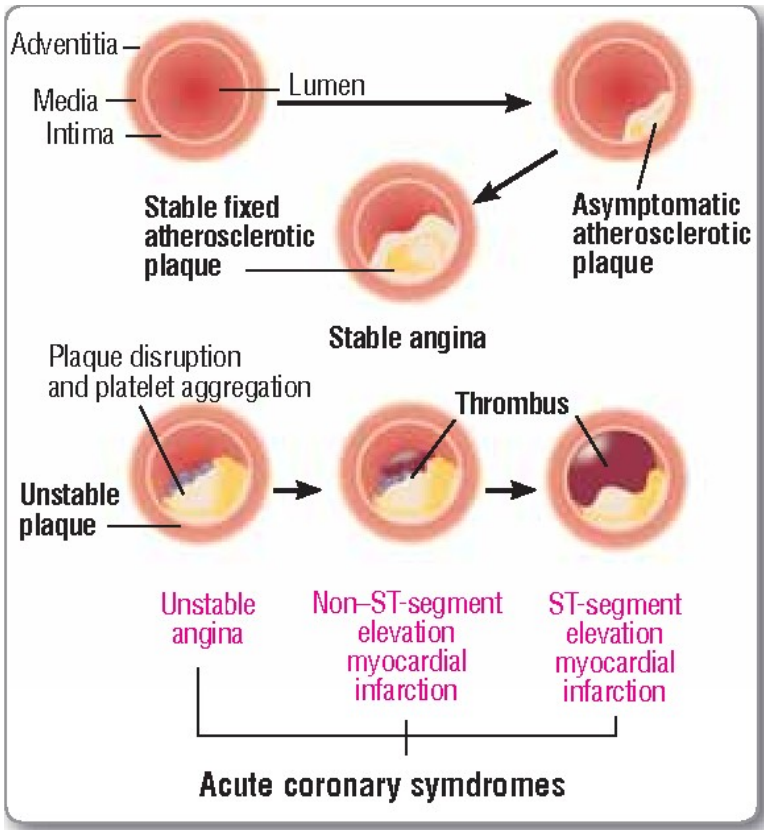

Figure 12: Acute coronary syndrome
(reproduced from: https://www.semanticscholar.org/paper/Acute-Coronary-Syndrome%3A-Focus-on-Antiplatelet-Bobadilla/2709d831008ee8f81d69c43cb1c90d95801b2374, Access 20.11.2019)

1.2.6 Cardiac Arrhythmia

Cardiac arrhythmia is defined as an irregular rhythm of the heartbeat. Based on the number of heart beats per minute, a distinction is made between bradycardic (< 60 beats/min) and tachycardic (> 100 beats/min) arrhythmias (47). Alterations in concentrations of ions and ion channel numbers as well as structural changes like cardiac hypertrophy and remodeling with loss of atrial myocardium, fibrosis and fatty infiltration facilitate the development of arrythmias. Most sustained arrhythmias are caused by reentry mechanisms and/or automaticity with abnormal impulse formation. With nearly 35% of all diagnosed arrhythmias, the most common sustained cardiac arrhythmia is atrial fibrillation (35). It is characterized by high-frequency excitation of the atrial myocadium which leads to unsynchronized atrial contraction and irregular excitation of the ventricles (48). The atrial rate is typically rapid with > 300 beats per minute. The ventricular rate, however, depends on atrioventricular node conduction and autonomic tone (35). The prevalence of AF is constantly increasing and is currently estimated around 1-4% in the USA, Europe and Australia. Given that, in the Western World, around 70% of people with AF are aged > 65 years, AF typically occurs later in life (49).

Major risk factors of AF are advanced age, hypertension and CAD. Hyperthyroidism, cor pulmonale, rheumatic heart disease, male sex and certain genetic variants are also associated with AF (35). Additionally, smoking, obesity, obstructive sleep apnea, sedentary lifestyle and diabetes mellitus are typical modifiable risk factors that predispose to AF**.** Most of these risk factors increase the susceptibility to AF through induction of histopathologic, electrical and structural changes of the atrium including inflammation, fibrosis, cellular and molecular changes (48).

Based on the pattern of occurrence atrial fibrillation can be classified as paroxysmal, persistent and permanent AF. While paroxysmal AF is short and self-limiting, persistent AF requires treatment in order to regain sinus rhythm and permanent AF typically persists despite medical interventions (50). In some cases paroxysmal AF progresses to persistent AF and persistent AF can also become permanent (48).

The clinical spectrum of AF ranges from completely asymptomatic or minimal symptoms to severe and disabling symptoms (50). The most frequently observed symptoms are palpitation, presyncope, fatigue and dyspnea. Chest pain and syncope are less common (35).

Finally, AF is associated with several adverse outcomes. Especially, stroke, as a consequence of AF, is a major concern when considering adequate treatment. On the one hand, the irregular rhythm in AF elicits the formation of a left atrial thrombus. On the other hand, other factors including abnormalities in coagulation and hemostasis, inflammation and endothelial dysfunction also contribute to a prothrombotic state and thrombogenesis and thereby increase the risk of AF-related stroke and other thromboembolic events.

Additionally, heart failure (HF) and MI are both, risk factors of AF as well as adverse cardiovascular consequences of AF. Especially, the association between HF and AF is well established. Both conditions share common risk factors and therefore often coexist, but also mutually predispose to one another (48).

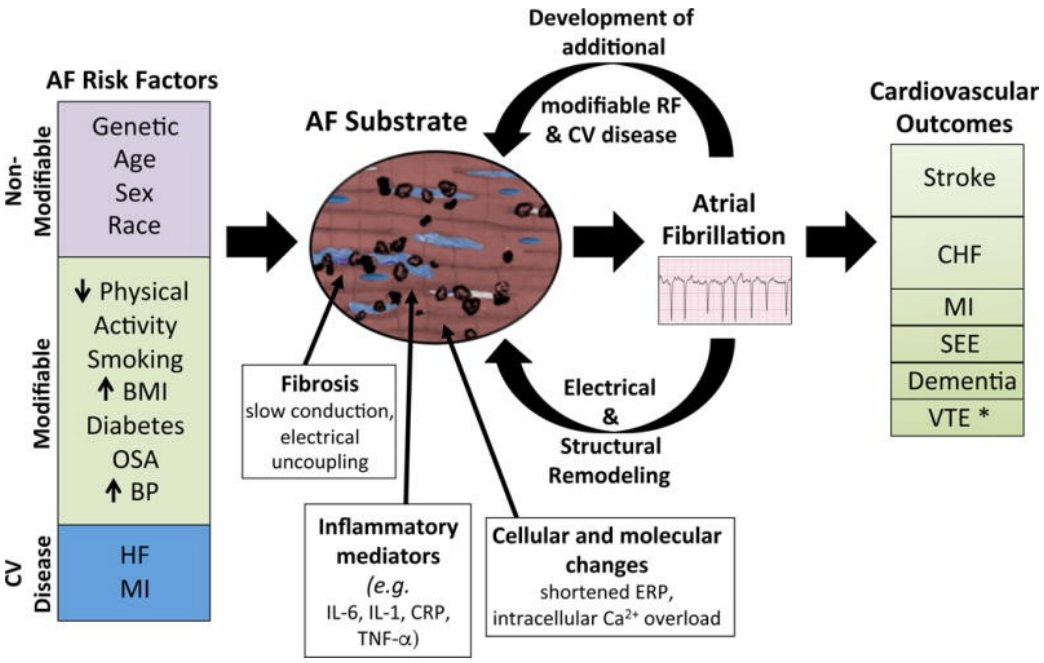

Figure 13: Risk factors, Development and Outcomes of AF
(reproduced from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5500874/, Access: 21.11.2019)

1.2.7 Heart failure

With more than 23 million people being affected globally, HF has become a major issue in the public health sector (51). It is typically a disease of individuals aged 60 and older and has a staggering five-year mortality rate of approximately 50%. The pathophysiology of heart failure is complex. HF is typically the consequence of structural or functional heart diseases. It is most commonly associated with a reduction of the left ventricular myocardial function which results in impaired ventricle filling and reduced cardiac output. However, pericardial, endocardial, valvular and vascular impairment can also be involved in the development of HF. Based on the location of the functional deficit, HF can be divided into left ventricular, right ventricular or biventricular HF. Left ventricular dysfunction may be the result of MI, whereas right ventricular dysfunction often develops on the basis of acute pulmonary embolism. Both may lead to insufficient cardiac output or low output failure (52).

Through assessment of the left ventricular ejection fraction (LVEF), it is possible to further specify left-ventricular HF. Impaired ventricular function with a LVEF < 40% is referred to as HF with reduced ejection fraction (HFrEF). A LVEF of more than 40% is classified as HF with preserved ejection fraction (HFpEF) (53).

Heart failure can be caused by a variety of factors and preceding conditions, of which the most common are CHD and arterial hypertension. Together they

account for three quarters of all HF cases (25). Other typical CV risk factors, such as diabetes, obesity, smoking, increased heart rate, chronic kidney disease and dyslipidemia also play an important role in the pathogenesis of HF. Less common causes of heart failure comprise, for example, infectious diseases, anemia, genetic predisposition, medication, alcohol and other toxins (54).

The pathophysiologic processes of HF are highly diverse and complex. It typically involves pressure overload of the heart, mainly due to hypertension, which leads to increased wall stress. Chronically increased wall stress subsequently induces myocardial hypertrophy, cell death through apoptosis and regeneration. Over time, these remodeling processes of the heart manifest as dilation of the ventricle and impaired contractile function, both result in insufficient cardiac output. Additionally, cardiac ischemia and infarction due to CHD or thrombosis can cause similar ventricular remodeling. Subsequently, the heart in no longer able to meet the metabolic demands of the body which cause a cascade of maladaptive responses including excessive neurohumoral and vascular stimulation through activation of SNS and RAAS. These mechanisms aim at sustaining cardiac performance, but in fact aggravate cardiac remodeling and further reduce cardiac function (53).

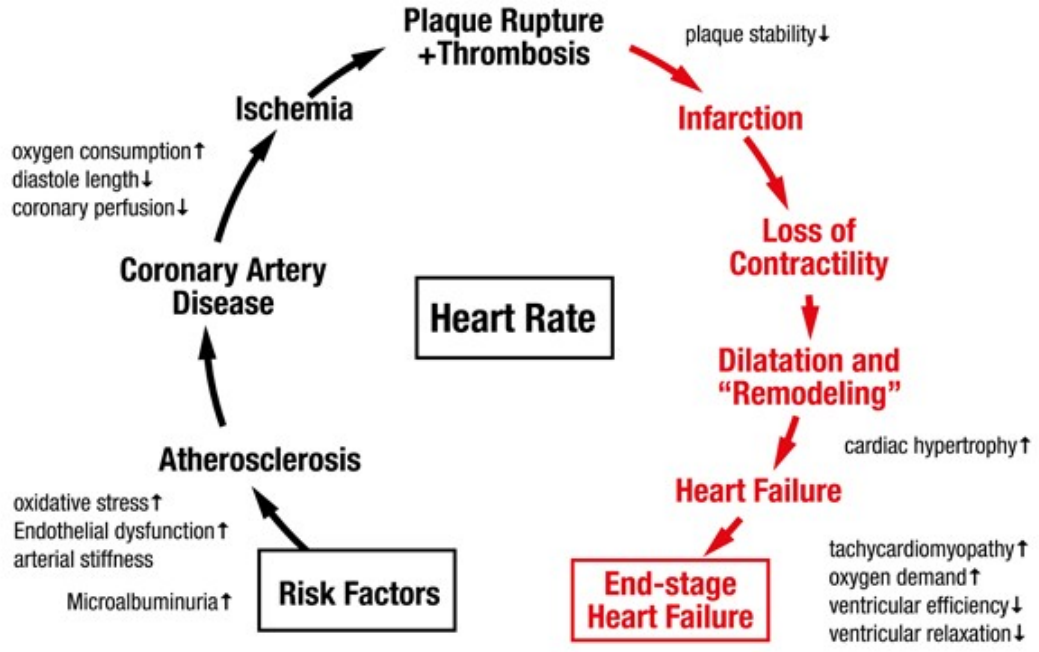

Figure 14: Development of heart failure
(reproduced from: https://www.shift-study.com/heart-rate-heart-failure/heart-rate-and-heart-failure/, Access 20.11.2019)

Heart failure is mainly a clinical diagnosis (51). Its clinical presentation typically includes dyspnea, paroxysmal nocturnal dyspnea, orthopnea, fatigue, edema, weakness, abdominal distention and pain in the upper right quadrant. Depending on the course of the disease and the time of onset, a distinction is made between acute and chronic heart failure (52). Additionally, morphological signs (increased LV mass) and biochemical indicators (TNF, IL-6, CRP, BNP and NT-BNP) can be used as tools of risk assessment and diagnosis of heart failure (54).

2 Aims and Objectives

Air pollution is an emerging global topic. More and more economies and nations are confronted with the increase in air pollution and its effects on healthcare systems.

While the harmful effects of air pollution on the respiratory system are widely known, there has been less attention towards the negative impact of air pollution on the cardiovascular system. Therefore, this diploma thesis aims at examining the effects of air pollution on the CVS in order to raise awareness of the harmfulness of air pollution in the context of CVDs. This thesis intends to provide a clear overview of relevant aspects, including pathways through which air pollutants interfere with the CVS. Special focus was placed on the relationship of air pollution and cardiovascular morbidity. For this purpose, correlations between exposure to air pollutants and changes in risk of developing CVDs were examined. An extensive review of the current literature was carried out to obtain the underlying mechanisms of air pollution and associated cardiovascular effects.

This topic is of particular relevance to people living and studying in Graz, since Graz is exceeding recommended threshold levels of various air pollutants on a regular basis (55) and therefore is often referred to as “Feinstaubhauptstadt Österreichs”.

Natural sources of air pollution only contribute a small amount, leaving air pollution a man-made problem. The fact that anthropogenic factors have the potential to be altered and improved, gives rise to hope. Considering air pollution as a modifiable risk factor of cardiovascular health provides the opportunity of intervention and prevention of cardiovascular outcomes.

3 Methodology

For this diploma thesis, the current literature on the subject of "effects of air pollution on the cardiovascular system" was systematically reviewed. Both primary and secondary sources of literature on the topic were examined. Additional information that was included in the introduction was obtained from textbooks, current guidelines and webpages of the World Health Organization, the European Environmental Agency and the American Heart Association. Further access to textbooks and relevant online material was primarily gained through the library of the Medical University of Graz.

PubMed, Web of Science and Google Scholar served as search engines and were used to look for and access relevant literature.

The first approach to the search for scientific publications on this topic showed an overwhelming number of search results with a total of over 800 entries. Following filters were therefore applied to narrow down the number of search results:

- Only articles that were available in a full version for free were taken into account.
- The publication date of considered articles was set at a limit of five years in order to ensure that the focus was laid on the latest findings and to further reduce the number of results.

Additionally, suggested articles had to fulfill following criteria in order to be selected:

- no cigarette smoke, only ambient and/or traffic-related air pollutants (TRAP) including the most prevalent pollutants: particulate matter (PM_{10}, $PM_{2.5,}$ UFPs), SO_2, NO_x, CO and ozone. Special focus was placed on PM, due to the fact that its concentration correlates strongly with cardiovascular morbidity and mortality.
- only cardiovascular, no cerebrovascular pathologies, no cardiopulmonary, no respiratory pathologies
- only human studies, no animal studies
- only articles in English or German

Adequate MESH terms were identified on PubMed, beforehand. For the search, it was made use of typical database search techniques, such as quotation, truncation, parentheses and the Boolean operators "AND", "OR" and "NOT" in

order to specify the search and to cover relevant synonyms and interchangeable terms.

Different combinations of following words and MESH terms were used when formulating the search:

“air pollution”, “particulate matter” or “PM”, “diesel exhaust”, “vehicle emission”, “cardiovascular”, “CVD”, “blood pressure”, “cardiac”, “cardiac arrhythmia”, “heart”, “coronary”, “atrial fibrillation” or “AF”, “short term”, “long term” and “mortality”.

Mendeley was chosen as citation program and used as a means to manage the references.

Since the topic of air pollution and its effects on the CVS is a very broad one, it was decided to further divide the search into different categories with each of them focusing on a specific cardiovascular issue.

Based on different aspects of cardiovascular consequences and the categorization used in other review articles, the search was further structured as follows:

- short-term effects of air pollution on the CVS
- long-term effects of air pollution on the CVS

The search for short-term effects of air pollution on the CVS resulted in 130 results. In comparison, approximately 50 publications dealt with long-term effects of air pollution.

Additional literature was gathered by scanning the bibliographic reference lists of the reviewed papers. This allowed for inclusion of relevant publications that were missed during the initial literature search.

Initially, the relevance and suitability of suggested articles was roughly determined by reading the articles´ abstracts. In a later step, the publications were read thoroughly, and their findings were structured and compared.

Proposed studies that focused on explanatory models involved in the association between air pollution and CVD (systemic inflammation, thrombogenicity, etc.) were collected separately. They were later included in “Section A” of the review in order to introduce and explain those proven or associated pathways to the reader.

Relevant images and figures were primarily obtained from papers and from webpages on this topic by using Google as a search engine.

4 Review of Current Literature

A total of 37 publications, consisting of clinical trials and review articles, were finally identified as relevant and included in the discussion.
Reviewing the relevant papers on the topic indicated that most of the current literature focuses on certain cardiovascular aspects. It was therefore decided to categorize the research articles by the following, most frequently evaluated, pathophysiological aspects and cardiovascular disorders:

- pathophysiological mechanisms and pathways
- blood pressure and incident hypertension
- acute coronary syndrome/ischemic heart disease and myocardial infarction
- atrial fibrillation or cardiac arrhythmia
- heart failure

Section A deals with potential mechanisms and pathways that may underly and explain the adverse effects of air pollution on the cardiovascular system. The findings of nine studies were included in this section (see Table 1).
In section B, nine publications that deal with changes in blood pressure and incident hypertension in the presence of air pollution were included (see Table 2).
Section C deals with the associations between air pollution and the risk of ACS, MI and IHD. The outcomes of eight studies are discussed in this section (see Table 3).
In section D the findings of six publications that deal with the effect of air pollution on the incidence of cardiac arrhythmia or atrial fibrillation were collected and compared with each other (see Table 4).
Section E elaborates on the relationship between air pollution and the risk of developing heart failure. Six studies provided relevant information on this topic (see Table 5).

4.1 Section A: Potential Mechanisms and Pathways

The cardiovascular outcomes discussed in this thesis share similar causes and pathogenic processes. The biological mechanisms underlying the relationship between air pollution and its adverse effects on the cardiovascular system are complex and mostly interlinked. Although some uncertainties are still remaining, a

considerable number of studies published in recent years has provided valuable insights into possible pathophysiological processes (5).

Table 1: Articles dealing with potential mechanisms and pathways

Author	Study Details	Results
Li et al. (2016)	clinical trial Framingham Offspring Cohort	positive association between $PM_{2.5}$ and biomarkers of **oxidative stress** (8- epi-PGF2a, myeloperoxidase)
Li et al. (2017)	clinical trial Framingham Heart Study	$PM_{2.5}$, BC, SO_4^{2-} positively associated with **CRP** levels, NO_x associated with higher levels of **IL-6**, no or negative associations with fibrinogen
Lanki et al. (2015)	clinical trial cross-sectional analysis ESCAPE project	positive associations between NO_x and **CRP**, no consistent associations between air pollution and fibrinogen levels
Pope et al. (2016)	clinical trial	$PM_{2.5}$ associated with increases of proinflammatory cytokines, monocytes, CD14+, CD16+, CD4+ and CD8+, augmented apoptosis of endothelial cells, reduced angiogenic properties of the plasma
Everson *et al*. (2020)	clinical trial follow-up: 6-months Cape Town, South Africa	negative association between individual long-term exposure to NO_2 and benzene and **LTL**: difference in LTL: **−7.30**% (95% CI, −10.98 to −3.46%) per 7.0 µg/m³ IQR increase in NO_2 and **−6.78**% (95% CI, −11.88 to −1.39%) per 3.3 µg/m³ IQR increase in benzene
Newby et al. (2015)	review article cross-sectional and longitudinal analyses included	$PM_{2.5}$ positively associated with formation and progression of **atherosclerosis**: increases in CIMT, IMT, CAC, TAC, AAC, ABI
Perez, Hazari and Farraj (2015)	review article	air pollutants elicit **autonomic dysfunction** through activation of baro-, chemo- and pulmonary reflexes
Robertson and Miller (2018)	review article	air pollution associated with **pro-coagulative** and **pro-thrombotic** states: platelet activation, impaired fibrinolytic processes, genetic and epigenetic changes
Xu et al. (2019)	clinical trial Beijing AIRCHD study	air pollution associated with increased **thrombogenicity** and **plaque vulnerability**: increased platelet activation, shortened prothrombin time, impaired fibrinolytic processes, circulating biomarkers of systemic inflammation

4.1.1 Oxidative stress and Systemic Inflammation

It is assumed that oxidative stress is a dominant factor involved in the pathogenicity of AAP (3,64). Observations by Li *et al*. (2016) support this hypothesis. In their community-based study, involving 2035 Framingham Offspring Cohort participants, they found a consistent positive association between $PM_{2.5}$ and sulfate with urinary creatinine-indexed 8-epi-prostaglandin F2a (8- epi-PGF2a) as well as between $PM_{2.5}$, BC and myeloperoxidase. 8- epi-PGF2a and myeloperoxidase are indicators of oxidative stress since both cause generation of ROS resulting in lipid peroxidation. Since lipid peroxidation is involved in platelet activation, vasoconstriction, endothelial dysfunction and plaque instability, it is further suggested that the rise in those two biomarkers of oxidative stress observed after short-term exposure to certain air pollutants, demonstrates a

potential link between air pollution and the associated cardiovascular pathologies (56).

As a part of the Framingham Heart Study, Li *et al*. (2017) additionally focused on the potential role of systemic inflammation as another intermediate mechanism explaining the cardiovascular events observed with increased levels of air pollution. Their findings demonstrated positive associations between short-term exposure to BC, $PM_{2.5,}$ SO_4^{2-} and CRP. Additionally, increased levels of NO_x were associated with elevated levels of interleukin-6 (IL-6). When assessing fibrinogen as an additional marker of systemic inflammation and coagulation, they found no associations between $PM_{2.5}$ and fibrinogen and even discovered that BC, NO_x and SO_4^{2-} were negatively associated with fibrinogen (57).

Similarly, Lanki *et al*. (2015), also evaluated fibrinogen levels and did not find consistent associations with air pollution. Their other findings, however, stand in contrast to Li *et al*. (2017). In their large cross-sectional analysis within the ESCAPE project, Lanki *et al*. (2015) observed positive associations between NO_x and CRP with an increase of 3.2% (95% CI; 0.3-6.1) per 20 µg/m^3 annual increase of $NO_{x.}$ Conversely, chronic exposure to particulate matter was not associated with increased levels of the biomarkers CRP and fibrinogen. These inconsistent findings suggest that the underlying pathways involving systemic inflammation and coagulation may vary depending on the temporal course and the kind of air pollution component (58).

Pope *et al.* (2016) have provided further evidence that $PM_{2.5}$ may be involved in triggering systemic inflammation and endothelial dysfunction subsequently leading to injury of the CVS. After being exposed to $PM_{2.5}$, study participants had higher levels of proinflammatory cytokines as well as monocytes, CD14+, CD16+, CD4+ and CD8+ circulating in the blood. $PM_{2.5}$ was furthermore associated with augmented apoptosis of endothelial cells and reduced angiogenic properties of the plasma. According to Pope *et al*. (2016), these findings may explain the atherogenic effects of PM involved in the pathophysiology of acute coronary events associated with air pollution (59).

In a recently conducted study, Everson *et al*. (2020) demonstrated that exposure to NO_2 and benzene is associated with shortening of telomeres, as measured by leukocyte telomere length (LTL). LTL indicates aging of cells and was linked to development of atherosclerosis. They detected a decline in LTL of −7.30% (95%

CI, −10.98 to −3.46%) per 7.0 µg/m³ IQR increase in NO_2 and −6.78% (95% CI, −11.88 to −1.39%) per 3.3 µg/m³ IQR increase in benzene. A further analysis showed that these effects of benzene and NO_2 on LTL equate a chronological cellular aging of 6.0 years and 10.3 years, respectively. These findings suggest that air pollution triggers acceleration of cellular aging and thereby may promote atherosclerosis and other degenerative processes affecting the CVS. It is assumed that inflammatory processes and oxidative stress are relevant mechanisms behind changes in telomere length. This study therefore provides an important link between the underlying molecular processes and the multiple adverse effects of air pollution observed in other studies (60).
Newby *et al*. (2015) further elaborated on the connection between air pollution and atherosclerosis in the expert position paper commissioned by the European Society of Cardiology. Mostly cross-sectional, but also longitudinal, analyses have shown a positive correlation between $PM_{2.5}$ and the formation and progression of atherosclerosis. Increases in atherosclerotic markers, namely carotid intima-media thickness (CIMT), intima-media thickness (IMT), coronary artery calcification (CAC), thoracic (TAC) as well as abdominal aortic calcification (AAC) and ankle-brachial index (ABI), have been linked to $PM_{2.5}$ exposure in an overwhelming number of publications (5).

4.1.2 Autonomic Imbalance

Perez, Hazari and Farraj (2015), provided a detailed overview of the existing evidence regarding the interference of air pollution with the ANS. According to Perez, Hazari and Farraj (2015), the mechanisms by which air pollutants elicit autonomic dysfunction mainly involve activation of baro-, chemo- and pulmonary reflexes. Studies included in the review have demonstrated that inhaled air pollutants act as irritants of pulmonary receptors. Triggering of the pulmonary reflex arc, in turn, are associated with changes in heart rate and blood pressure, cardiac arrhythmia and ST segment depression. Other studies described by Perez, Hazari and Farraj (2015), support the idea that exposure to air pollution leads to reduced baroreceptor sensitivity. This desensitization of the baroreflex results in changes in the autonomic tone, which may partly explain increases in BP due to enhanced activity of the SNS. Given that these autonomic reflex arcs are highly interconnected with the CVS and also interact with one another, Perez,

Hazari and Farraj (2015) emphasize the variety of possible pathways responsible for air pollution-related disturbances in the ANS and associated cardiovascular disorders. According to Perez, Hazari and Farraj (2015), most studies have focused on assessing heart rate variability as an indirect marker of air pollution-mediated changes in ANS-activity. Perez, Hazari and Farraj (2015) noted that exposure to air pollution has surprisingly been linked to both, increased and reduced HRV. It is unclear why this tendency varies. Nevertheless, the changes in HRV still reflect autonomic imbalance and therefore provide evidence that air pollution has the capacity to interfere with the ANS and thereby may contribute to adverse cardiovascular outcomes (61).

4.1.3 Thrombogenicity

Robertson and Miller (2018) published an updated review of the current literature existing about air pollution-mediated thrombosis. Despite some remaining inconsistencies, there is substantial evidence for the pro-thrombotic effects of air pollution. According to Robertson and Miller (2018), several mechanisms that are involved in a shift towards a pro-coagulative or pro-thrombotic state were identified. They describe enhanced platelet activation, impaired fibrinolytic processes and oxidative stress and inflammation as major underlying factors. Additionally, some of the included studies indicate that genetic and epigenetic alterations may determine the degree of susceptibility to the pro-thrombotic effects of air pollution. Particulate matter, especially $PM_{2.5}$, was found to have the strongest pro-thrombotic effects. They argue that the hemostatic changes caused by particulate pollutants may contribute to thrombotic events, myocardial ischemia and other adverse cardiovascular outcomes. However, it is not clear whether gaseous constituents of air pollution also promote hemostasis and thrombosis (62).

As part of the Beijing AIRCHD study, Xu *et al*. (2019) observed that acute exposure to elevated levels of air pollution is associated with increased vulnerability of atherosclerotic plaques and heightened thrombogenicity. Similarly to Robertson and Miller (2018), the study results demonstrated elevated markers of plaque vulnerability, increased platelet activation, shortened prothrombin time and altered fibrinolytic processes. Furthermore, circulating biomarkers of systemic inflammation were also elevated. Inflammatory pathways were additionally found

to play a substantial role in mediating the changes in plaque stability and thrombogenicity observed with air pollution. By linking air pollution to pro-thrombotic conditions, these studies provide further insights into the pathophysiologic mechanisms through which air pollution may contribute to CV morbidity and mortality (63).

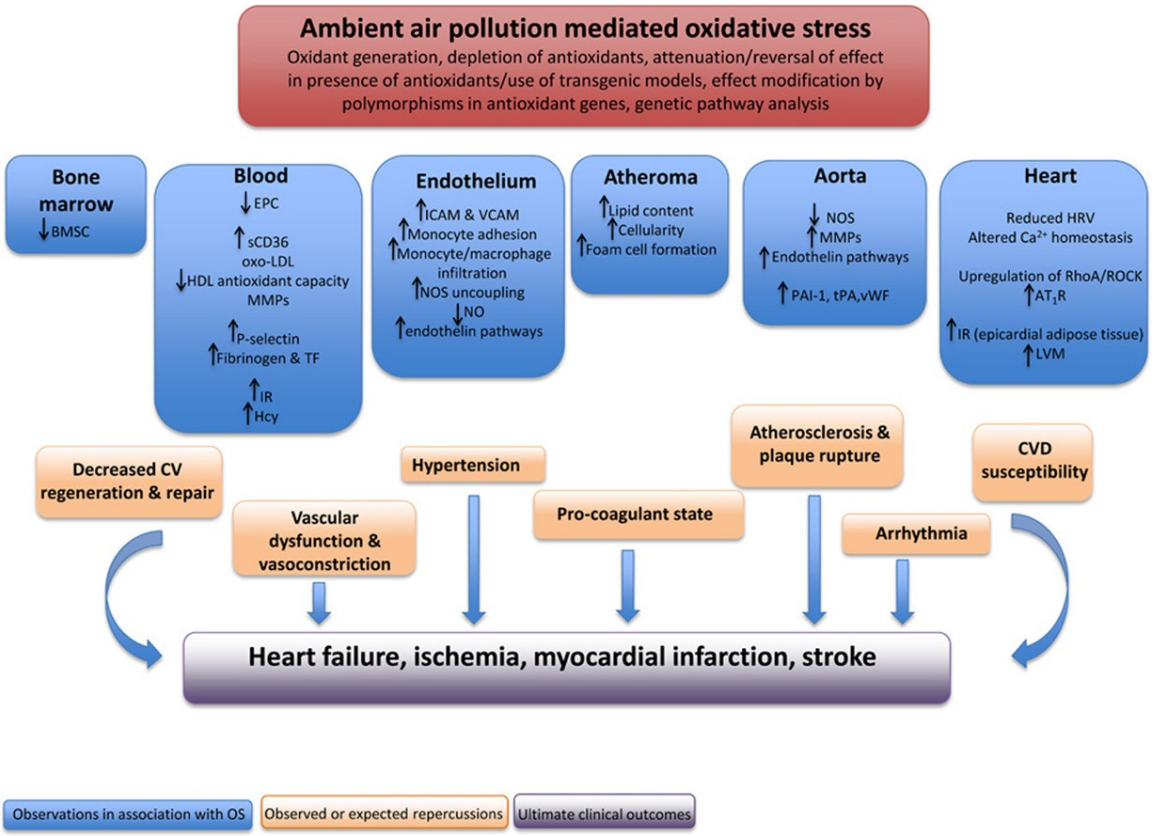

Figure 15: Summary of pathophysiological mechanisms
(reproduced from: (65))

4.2 Section B: Air Pollution and Blood Pressure/Incident Hypertension

Given that hypertension is a crucial predisposing factor for almost all acquired CVD including CHD, cardiac arrhythmias and cardiac valve diseases (23), numerous studies have indicated that changes in BP may be a crucial factor linking aforementioned processes, such as endothelial dysfunction as well as imbalance of the ANS, to negative cardiovascular outcomes associated with air pollution (5,64,66).

A meta-analysis regarding the link between air pollution and the incidence of hypertension was performed within the course of the European Study of Cohorts for Air Pollution Effects (ESCAPE). Their analysis of the impact of long-term

residential exposure to TRAP on BP demonstrated a weak positive association with SBP, DBP and prevalent hypertension (see Table 2). The OR for hypertension prevalence per 5 μg/m^3 increase of $PM_{2.5}$ was estimated 1.07 (95% CI, 0.95-1.21) (68).

Table 2: Articles dealing with association between air pollution and BP or incident HT

Author	Study Details	Exposure	Results
Cai et al. (2016)	systematic review and meta-analysis	**short-term long-term**	significant associations between HT and short-term exposure to air pollutants (per 10 μg/m^3 increase): SO_2 OR=**1.046** (95% CI, 1.012-1.081) $PM_{2.5}$ OR=**1.069** (95% CI, 1.003-1.141) PM_{10} OR=**1.024** (95% CI, 1.016-1.032) significant associations between HT and long-term exposure (per 10 μg/m^3 increase): NO_2 OR=**1.034** (95% CI, 1.005-1.063) PM_{10} OR=**1.054** (95% CI, 1.036-1.072) positive associations (but not statistically significant) between short-term exposure to NO_2, O_3, CO and long-term exposure to NO_x, $PM_{2.5}$, and SO_2
Fuks et al. (2014)	*ESCAPE project,* meta-analysis, cross-sectional, 15 population-based cohorts, N=164484, Europe	**long-term**	increased SBP and DBP in nonmedicated participants (per 4,000,000 vehicles × m/day): SBP increase: **0.35** mmHg (95% CI, 0.02-0.68) DBP increase: **0.22** mmHg (95% CI, 0.04-0.40) (per 5μg/m^3 increase in $PM_{2.5}$): SBP increase: **0.20** mmHg (95% CI, -0.76-1.16) DBP increase: **0.14** mmHg (95% CI, -0.57-0.85) estimated OR for prevalent hypertension: • per 5 μg/m^3 of $PM_{2.5}$: **1.07** (95% CI, 0.95-1.21) • per 4000000 vehicles × m/day: **1.05** (95% CI, 0.99-1.11) no clear association between modeled air pollutants and BP
Huang et al. (2018)	repeated measures panel study N = 50 (Michigan) N = 73 (Beijing)	**short-term**	per 10 μg/m^3 increase in outdoor-ambient $PM_{2.5}$ during prior 1-7 days: Beijing: significant increase in DBP (**0.15-0.17** mmHg) Michigan: not associated with increase in BP increased susceptibility: overweight
Corlin et al. (2018)	*CAFEH study* cross-sectional, N=409, near Boston, Massachusetts	**long-term**	positive, non-significant associations between annual average UFPs (TAA-PNC) and: SBP (β = **5.23**, 95% CI, -0.68-11.14 mmHg) PP (β = **4.27**, 95% CI, -0.79-9.32 mmHg) HT (OR = **1.81**, 95% CI, 0.94-3.48) no positive association with DBP (β = **0.96**, 95% CI, -2.08-4.00 mmHg) increased susceptibility: non-Hispanic white participants, diabetics
Z. Zhang et al. (2018)	cohort study, N=361560, follow-up: 2001-2014, Taiwan	**long- term**	per 10 μg/m^3 increase in the 2-y average $PM_{2.5}$ concentration: SBP-increase: **0.45** mmHg (95% CI, 0.40-0.50) DBP-increase: **0.07** mmHg (95% CI, 0.04-0.11) PP-increase: **0.38** mmHg (95% CI, 0.33-0.42) risk of developing hypertension **3%** [HR=1.03 (95% CI, 1.01-1.05)]
Lin et al. (2017)	cohort study, N=12665, China	**long-term**	adjusted OR for hypertension **1.14** (95% CI, 1.07-1.22) per 10 μg/m^3 increase in annual average $PM_{2.5}$ **11.75**% (95% CI, 5.82-18.53%) of hypertension cases in the study cohort attributable to ambient $PM_{2.5}$ increased susceptibility: overweight/obesity decreased susceptibility: consumption of fruit

Foraster et al. (2014)	*REGICOR study* population-based cohort study, N=3700, Spain	**long-term**	positive association between NO_2 and SBP in nonmedicated individuals: SBP-increase: **1.34** mmHg (95% CI, 0.14-2.55) per 10 µg/m^3 increase in NO_2 NO_2 not associated with HT (when adjusted for transportation noise)
Z. Zhang *et al.* (2016)	*Nurses' Health Study,* N=74880, follow-up: 1988 -2008	**long-term**	increased incidence of HT (per 10 µg/m^3 increase in 2y-average of PM_{10}, $PM_{2.5}$ and $PM_{2.5-10}$): PM_{10} HR: **1.02** (95% CI, 1.00-1.04) $PM_{2.5}$ HR: **1.04** (95% CI, 1.00-1.07) $PM_{2.5-10}$ HR: **1.03** (95% CI, 1.00-1.07) increased susceptibility: < 65 years, obesity
Everson et al. (2019)	N=61 (all females) follow-up: 6-months, Cape Town, South Africa	**long-term**	positive association between NO_2 and SBP and DBP (per 4.96 µg/m3 increase in NO_2) SBP-increase: **2.42** mmHg (95% CI, 0.03-4.80 mmHg) DBP-increase: **1.76** mmHg (95% CI, 0.00-3.52 mmHg) negative association between NO_2 and mean baseline brachial diameter and CRVE DBP-increase: **2.07** mmHg (95% CI, 0.06-4.07 mmHg) per 2.56 µg/m3 increase in total BTEX cIMT-increase: **24.88** µm (95% CI, 2.19-47.57 µm) per 2.08 µg/m3 increase in benzene

Another important overview regarding this matter was given by Cai et al. (2016). Their meta-analysis incorporates 17 studies and investigated the effects of acute and chronic exposure to PM_{10} and $PM_{2.5}$, ozone, CO, SO_2 and NO_x. Although all air pollutants were shown to positively correlate with hypertension, the risk of hypertension was only significantly increased after short-term exposure to PM and SO_2 as well as long-term exposure to PM_{10} and NO_2 (69).

Z. Zhang *et al*. (2016) obtained similar results with their analysis of long-term exposure to $PM_{2.5}$, $PM_{2.5-10,}$ PM_{10} and self-reported hypertension as part of the Nurses' Health Study. The impact on hypertension incidence was strongest for $PM_{2.5}$ with a hazard ratio of 1.04 (95% CI, 1.00-1.07) per 10 µg/m^3 increase in 2-year average $PM_{2.5}$ concentration. As shown in Table 2 the association was smaller with PM_{10} and $PM_{2.5-10}$ (67).

The results of Lin et al. (2017) and Z. Zhang et al. (2018) indicate as well that $PM_{2.5}$ may be considered a possible causative agent of hypertension. According to Zhang et al. (2018), each 10 µg/m^3 increase in 2-year average $PM_{2.5}$ leads to a 3% risk increase of hypertension, which is very similar to the estimation of Zhang et al. (2016) (70). The analysis of Lin et al. (2017) showed that 11.75% (95% CI, 5.82-18.53%) of the incident cases of hypertension in their study cohort might be attributed to long-term exposure to $PM_{2.5}$. This suggests that the contribution of ambient $PM_{2.5}$ to the hypertension burden might be even more pronounced (71).

A recently published study by Huang et al. (2018) was aimed at comparing two cities, Beijing and Michigan, that differ greatly in the level of air pollution. Their results also suggested that $PM_{2.5}$ might have particularly BP altering qualities occurring acutely after exposure. However, a significant response was only observed with DBP which rose by 0.15-0.17 mmHg per 10 µg/m^3 increase in $PM_{2.5}$. Additionally, this observation seemed to be limited to participants from Beijing, suggesting that comparatively low concentrations of PM, as in Michigan, do not result in BP elevations (66).

Conversely, along with Fuks et al. (2014) and Z. Zhang et al. (2018), greater associations with SBP were found by Corlin et al. (2018). The focus of their Community Assessment of Freeway Exposure and Health (CAFEH) study was on the role of UFPs in the context of BP alterations. Their precise calculations included time-activity-adjusted particle number concentrations (TAA-PNC) as a means of assessing individual long-term exposure to UFPs with a high spatial resolution of 20 meters and a temporal resolution of one hour. TAA-PNC exposure positively, but non-significantly correlated with hypertension prevalence, SBP and pulse pressure (PP). They found less association with DBP (72). Their findings indicate that the impact of air pollution on BP may vary with particle size and pollutant type.

Everson et al. (2019) provided further insights into the relationship between AAP and BP alterations. They monitored 7-day individual exposure of female residents of Cape Town, South Africa to the gaseous air pollution components BTEX (benzene, toluene, ethyl-benzene and m+p- and o-xylenes) and NO_2. The results of this study demonstrated a positive association between NO_2 and increases in both SBP and DBP (see Table 6). Moreover, exposure to NO_2 was linked to reduction in diameters of blood vessels, as measured by mean baseline brachial diameter and central retinal venular equivalent (CRVE). According to Everson et al. (2019), these changes in vessel tone add further evidence that certain air pollutants cause vasoconstriction, probably by interfering with the ANS, and thereby influence BP levels. Other findings of this study suggest that exposure to BTEX also increases DBP. A significant increase in DBP of 2.07 mmHg (95% CI, 0.06-4.07 mmHg) was observed per 2.56 µg/m3 increase in total BTEX. Furthermore, an assessment of cIMT showed an increase in cIMT of 24.88 µm (95% CI, 2.19-47.57 µm) with each increment of 2.08 µg/m^3 in benzene, indicating

that exposure to benzene promotes atherosclerosis, which in turn is closely linked to BP elevations and hypertension (73).

Some of the described studies performed an additional assessment of effect modification. Interestingly, Z. Zhang et al. (2016), Lin et al. (2017) and Huang et al. (2018) all found that overweight or obese individuals seem to be more vulnerable to the prohypertensive effects of air pollutants (66,67,71). Additionally, Corlin et al. (2018) described a higher susceptibility in diabetics and non-Hispanic white participants, suggesting that there may be differences in vulnerability depending on ethnicity (72).

4.3 Section C: Air Pollution and Coronary Heart Disease/Ischemic Heart Disease and Myocardial Infarction

In the last years, several articles focused on the link between exposure to particulate air pollution and incidents of ACS, MI or IHD. Supported by the findings of those publications, there is more and more evidence of air pollution, and especially particulate air pollution, correlate with a higher risk for different forms of myocardial ischemia.

Table 3: Articles dealing with association between air pollution and CAD/IHD/MI

Author	Study Details	Exposure	Results
Q. Zhang *et al.* (2016)	case-crossover, N= 2749 Beijing, China	**short-term**	increase in risk of ERVs for STEMI per 10 µg/m^3 increase in $PM_{2.5}$: OR=**1.05** (95% CI, 1.00-1.11) no effects found for NSTEMI and PM_{10} increased susceptibility: ≥65 years
Pope *et al.* (2015)	time-stratified, case-crossover N=16314 urban areas of Wasatch Front, Utah, USA	**short-term**	increase in risk per 10 µg/m^3 increase in $PM_{2.5}$: total ACS: **6%,** STEMI: **15%**, UA: **9%**, NSTE-ACS: **5%** increased susceptibility for STEMI: hyperlipidemia, < 65 years, men, smokers
Gardner et al. (2014)	case-crossover N= 777 Rochester, New York, USA	**short-term**	increase in risk of STEMI per 7.1 µg/m^3 increase in $PM_{2.5}$: **18%** no effects found for NSTEMI increased susceptibility: CVD, hypertension, non-smokers, ≥ 65 years, Caucasians, women
W. Zhang *et al.* (2018)	case-crossover N=1922918 New York, USA	**short-term**	excess rate of hospital admissions for IHD per IQR increase in $PM_{2.5}$: **2.8%** (95% CI, 1.5-4.0%) and for MI: **2,3%** (95% CI, 0.5-4.0%)
Xu *et al.* (2017)	N= 56221 urban areas of Beijing	**short-term**	increase of daily ERVs for IHD per 10 mg/m^3 increase in $PM_{2.5}$: **0.56%** (95% CI, 0.16-0.95%) increased susceptibility: < 65 years, temperature > 11.01°C, no differences in gender
Ye *et al.* (2016)	N= 604944 Shanghai, China	**short-term**	increase in risk of outpatient visits and ERVs for CHD: $PM_{2.5}$ (per 10 µg/m^3 increase): **0.74%** (95% CI, 0.44-1.04%) PM_{10} (per 10 µg/m^3 increase): **0.23%** (95% CI, 0.12-0.34%) increased susceptibility: men, ≥ 65 years
Cesaroni *et al.* (2014)	data from ESCAPE-study,	**long-term**	increased risk of acute coronary events (MI, UA): $PM_{2.5}$ (per 5 µg/m^3 increase in annual mean): HR **1.13**

	large European multicentre study (Finland, Sweden, Denmark, Germany, Italy)		(95% CI, 0.98-1.30) PM_{10} (per 10 µg/m^3 increase in annual mean): HR **1.12** (95%CI, 1.01-1.25) other pollutants: positive but non-significant effects increased susceptibility: > 60 years
Kim et al. (2017)	population-based study N= 136094 follow-up: 7 years Seoul, South Korea	**long-term**	increased risk of AMI per 1 µg/m^3 increment in $PM_{2.5}$: HR **1.36** (95% CI, 1.19-1.56) negative effects found with PM-coarse, CO, SO_2, NO_2 increased susceptibility: women, < 65 years

Comparing the main findings of these studies showed that, when evaluating the incidences of MI, it is important to assess the incidences of STEMI and NSTEMI separately. Q. Zhang *et al*. (2016), for example, did not find any significant changes in total numbers of AMI, but when looking at the specific numbers of STEMI and NSTEMI they did observe that the risk of STEMI was significantly increased by every 10 µg/m^3 increase of $PM_{2.5}$ concentration [OR 1.05 (95% CI, 1.00-1.11)] (74). The number of NSTEMI, however, showed no association with elevated $PM_{2.5}$ levels. Similar findings were also observed in the investigations by Pope *et al*. (2015) and Gardner *et al*. (2014) where a clear distinction between STEMI and NSTEMI was made as well (75,76). One possible explanation for this difference in risk was discussed by Gardner *et al*. (2014) who suggested that particulate air pollution might cause an imbalance between thrombogenic and thrombolytic processes. By inhibiting thrombolysis or, alternatively, by causing excessive clot formation, PM might have aggravating effects that lead to more serious cases of AMI, hence STEMI (76). Q. Zhang *et al*. (2016) also mentioned another plausible explanation for higher incidences of STEMI associated with air pollution: Higher levels of $PM_{2.5}$ combined with pre-injured coronary arteries and destabilized plaques increase the likelihood of complete vessel occlusion and sever ischemia of the myocardium seen in STEMI.

There is particular interest in the comparison between acute coronary events that occur immediately after exposure to air pollution and those that were observed after a longer period of time. One underlying idea of comparing short-term to long-term effects, was to gain informative results that provide insight into the pathophysiological processes behind air pollution as a trigger of myocardial ischemia.

Studies by Pope *et al*. (2015), Gardner *et al.*(2014) and Q. Zhang *et al*. (2016) all focused on the short-term effects of increased PM-concentrations. Study results of

Q. Zhang *et al*. (2016) showed that higher levels of $PM_{2.5}$ are linked to a greater risk of STEMI with a time lag of one day. Pope *et al*. (2015) were able to demonstrate similar effects. They observed an increased risk of 8-15% of STEMI for every 10 µg/m^3 increment in $PM_{2.5}$ concentration on the same day as exposure (75). The results of Gardner *et al*. (2014) even suggest that elevated $PM_{2.5}$ concentrations immediately trigger STEMI in patients one hour after being exposed. This instant effect was demonstrated with a 7.1 µg/m^3 increase of $PM_{2.5}$ that resulted in a rapid increase of relative risk of STEMI by 18% (76).
Investigating the number of ERVs and hospital admissions provided further evidence that some of the effects associated with elevated PM concentrations occur within a relatively short time frame. W. Zhang *et al*. (2018) observed an excess rate of 1,3% and 1.0% of hospital admissions for IHD and MI, respectively, on lag days 0-4 that were attributed to elevated $PM_{2.5}$ concentrations (77). Similarly, the study results by Xu *et al*. (2017) showed that a rise of $PM_{2.5}$ by 10 µg/m^3 increased the number of emergency department visits for IHD by 0,56% at lag day 0-1 (78).
Ye *et al*. (2016) put the focus on CHD in an outpatient as well as emergency room setting and gained similar results. The largest changes in the number of ERVs for CHD was seen at lag day 0 with an increase of 0.74% for every 10 µg/m^3 increase in $PM_{2.5}$ (79).
These findings suggest that there are rapidly ongoing processes by which PM exacerbates CHD or even provokes STEMI.
Such underlying processes are listed and examined in more detail in Section A, but potentially include acute destabilization of preexisting plaques resulting in plaque ruptures and clot formation followed by occlusion of coronary arteries and thromboembolic events. Additionally, the instant induction of vasoconstriction elicited by PM might be another plausible pathomechanism accounting for the very short time interval between PM-exposure and occurrence of STEMI (75,76).
In addition to those consequences that occur shortly after PM-exposure, similar adverse effects were observed in people who were exposed to air pollution over a prolonged period of time. Effect estimates were highest for $PM_{2.5}$. An increase of annual $PM_{2.5}$ levels of 5 µg/m^3 was shown to increase the risk of acute coronary events by 13% (80). Similarly, Kim *et al*. (2017) also researched the long-term

effects of PM and observed a 30 to 36% increase in the incidence of MI for every 1 µg/m^3 increment of $PM_{2.5}$ (81).

It was possible to identify certain patient subgroups that showed higher susceptibility and therefore a higher risk of air pollution-induced STEMI. Especially participants with preexisting coronary artery disease as well as those with a medical history of cardiovascular events and hypertension are more prone to air pollution-related acute ST-elevation myocardial infarction. In addition, hyperlipidemia is seen as a separate risk factor (75,76).

Some contradictory results were found concerning gender, certain age groups and smoking as a risk factor. Women and Caucasians tend to be more affected, according to Gardner *et al.* (2014), although some conflicting findings were provided by Ye *et al*. (2016) suggesting that men have a higher risk of air pollution-related IHD.

In the study conducted by Pope *et al*. (2015) younger participants as well as smokers were more susceptible, whereas in the study of Gardner *et al*. (2014) non-smoking patients and those who were older than 65 years showed a higher risk. Similarly, Cesaroni *et al*. (2014) identified those > 60 years and Ye *et al*. (2016) those > 65 years to be at greater risk. However, the results of Q. Zhang *et al*. (2016) only showed effect alterations in those > 65 years, but for no other subgroup, and the study results of Kim *et al*. (2017) did not show any differences regarding any of the aforementioned factors.

4.4 Section D: Air Pollution and Atrial Fibrillation/Cardiac Arrhythmia

Given the high prevalence of cardiac arrhythmia and its most common form, atrial fibrillation, it becomes increasingly important to understand the underlying causes and aggravating factors that lead to disturbances of the heart rhythm (82,83). With the intent of providing insight into the connections between air pollution and cardiac arrhythmia numerous investigations were carried out in the last decades six recent studies regarding this matter have met the inclusion criteria of this literature research and will therefore be discussed hereafter.

Zhao *et al*. (2014) followed by Zheng *et al*. (2018) both conducted extensive studies regarding this matter in China, a country that is known for its high concentration levels of air pollutants. The main focus of Zhao *et al*. (2014) lied on

investigating potential associations between levels of PM_{10}, SO_2 and NO_2 and numbers of outpatient visits due to cardiac arrythmia. Their results demonstrated a significant increase of arrhythmia-related outpatient visits, particularly on the same day as exposure to elevated levels of air pollution (see Table 4). However, the impact of increased air pollutants seemed to decline in the following days (lag 1 and 2 days). NO_2 showed the strongest and most long-lasting effects, suggesting a greater risk of AF caused by gaseous pollutants (84).

Table 4: Articles dealing with association between air pollution and atrial fibrillation/cardiac arrhythmia

Author	Study Details	Exposure	Results
Zhao *et al.* (2014)	time-series analysis N=56940 central urban district in Shanghai, China	**short-term**	increased number of outpatient visits for arrhythmia per 10 µg/m^3 increase in concentrations of: PM_{10}: **0.56%** (95% CI, 0.42-0.70%) SO_2: **2.07%** (95% CI, 1.49-2.64%) NO_2: **2.90%** (95% CI, 2.53-3.27%) increased susceptibility: ≥ 65 years, women
Zheng *et al.* (2018)	case-crossover N=175265 26 cities in China	**short-term**	increased risk of hospital admissions for cardiac arrhythmia: $PM_{2.5}$ (per IQR increase of 47.5 µg/m^3): **2.09%** (95% CI, 1.58-2.60%) PM_{10} (per IQR increase of 76. 9 µg/m^3): **2.33%** (95% CI, 1. 68-2.97%) NO_2 (per IQR increase): **2.45%** (95% CI, 1.73-3.17%) CO (per IQR increase): **2.79%** (95% CI, 2.20-3.39%) increased susceptibility: > 65 years, diabetes
Solimini and Renzi (2017)	14 years-time-series analysis N=79892 Rome, Italy	**short-term**	increased number of daily hospital emergency visits for AF: $PM_{2.5}$: **2.95%** (95% CI, 1.35-4.67%) PM_{10}: **1.44%** (95% CI, 0.65-2.26%) NO_2: **1.19%** (95% CI, 0.27-2.13%) susceptibility: > 75 years, men
Monrad *et al.* (2017)	N=2700 Danish Diet, Cancer and Health study, Denmark	**long-term**	increased risk of hospital admissions for AF per 10 µg/m^3 NO_2: **7%** in 1-year follow-up **8%** in 5-year and 10-year follow-up no clear tendencies regarding effect modification by sex, smoking, HT or MI.
Stockfelt *et al.* (2017)	GOT-MONICA cohort: N=4500, PPS cohort: N=5850, Gothenburg, Sweden	**long-term**	no positive association between long-term exposure to air pollution and the incidence of AF (lag day 1-5) PPS: PM_{10}: HR=**1.07** (95% CI, 0.83-1.39), $PM_{2.5}$: HR=**1.09** (95% CI, 0.84-1.42) GOT-MON: PM_{10} HR=**0.63** (95% CI, 0.37-1.08), $PM_{2.5}$: HR=**0.46** (95% CI, 0.28-0.75)
Song *et al.* (2016)	meta-analysis, systematic review 23 studies Asia (China), Europe, North America, Brazil	**short-term**	increased number of hospitalizations/mortality for arrhythmia: $PM_{2.5}$ (per 10 µg/m^3): RR=**1.015** (95% CI, 1.006-1.024) PM_{10} (per 10 µg/m^3): RR=**1.009** (95% CI, 1.004-1.014) CO (per 1 ppm): RR=**1.041** (95% CI, 1.017-1.065) SO_2 (per 10 ppb): RR=**1.021** (95% CI, 1.003-1.039) NO_2 (per 10 ppb): RR=**1.036** (95% CI, 1.020-1.053) no association with ozone: RR=**1.012** (95% CI, 0.997-1.027 per 10 ppb)

Zheng *et al*. (2018) used a large database from 26 different Chinese cities in their multisite study. Similarly to Zhao *et al*. (2014) , they investigated the acute effects of air pollution by evaluating the number of hospitalizations related to cardiac arrhythmia. In the study they found a significant correlation between the concentration levels of $PM_{2.5}$ and PM_{10} and the number of daily hospitalizations for cardiac arrhythmia. Every 10 µg/m^3 increase in $PM_{2.5}$ was linked to a 0.44% greater risk of arrhythmia-associated hospital admissions, which, in turn, accounted for a 2,09% increase of risk observed with an interquartile range (IQR) increment of $PM_{2.5}$. Similarly, the number of hospitalizations for cardiac arrhythmia increased by 0.30% for each 10 µg/m^3 increment in PM_{10}. When observing the effects of $PM_{2.5}$ over a period of three days, the impact cumulated and resulted in a total increase of risk of 2.93%. The biggest effect was observed after a period of two days (85). Nevertheless, the results regarding different time intervals in which air pollution seems to have the largest effect on the incidence of AF show considerable inconsistencies. In the study of Solimini and Renzi (2017), for example, heightened levels of PM_{10}, $PM_{2.5}$ and NO_2 were correlated with hospital emergency visits for AF. This effect, however, was only observed immediately within one day after exposure (lag 0-1 day). Among the three investigated air pollution components, $PM_{2.5}$ seemed to have the most significant impact, whereat the number of ERVs for AF associated with $PM_{2.5}$ showed an increase of 3%. In contrast to the study of Zheng *et al*. (2018), this positive association was not seen on day 2-5 following exposure, suggesting that the effect is rather immediate than cumulative in nature (83).

Until recently, most studies on this subject have only investigated the influence of short-term exposure to air pollutants on the risk of developing AF. The study of Monrad *et al*. (2017) was the first to particularly focus on the long-term effects of TRAP on the incidence of AF. They used the data of a large cohort of citizens of Aarhus and Copenhagen from the Danish Diet, Cancer, and Health study. Ultimately, they were able to include 2700 cases of patients that were hospitalized due to new-onset AF. They chose NO_2 and NO_x for the assessment of TRAP arguing that those two components show close correlation with PM, and thus are regarded as reliable markers. However, the choice of these indicators leads to considerable difficulties in comparing their results with others, considering that usually particulate matter ($PM_{2.5}$, PM_{10}, UFPs) is used to evaluate air pollution.

They had an average follow-up of 14.7 years and opted for a 1-year, 5-year and 10-year exposure window. Both, in the 5-year and the 10-year follow-up, their results showed an 8% increase in risk of AF per every 10µg/m^3 increment of mean NO_2. Similarly, the number of AF incidences associated with the same increase in NO_2 concentration rose by 7% during the 1-year follow-up period. The effects observed with chronic NO_x exposure were generally similar, but weaker (86). Another European study which investigated the long-term effects of air pollution was published by Stockfelt *et al*., 2017. In addition to NO_x, they also looked at the impact of total and source specific particulate matter (PM_{10} and $PM_{2.5}$). Three different time spans were evaluated: directly at study start, last year of exposure and previous five years. In their study population, consisting of two Swedish cohorts, they identified 1712 cases of AF. In contrast to Monrad *et al.*, 2017, their final analysis did not show a positive correlation between chronic exposure to air pollution and the incidence of AF. In the study the overall exposure levels to PM were moderate with a median concentration of 9 µg/m^3 for $PM_{2.5}$ and 13 µg/m^3 for PM_{10}, which may account for their result (88).

Song *et al*. (2016) were among the first who conducted a meta-analysis and a systematic review on this subject. By collecting and comparing data from a total of 23 studies that were published until 2015 they were able to demonstrate that both particulate (PM_{10}, $PM_{2.5}$) and gaseous (NO_2, NO, SO_2) constituents of air pollution are associated with an increased risk of hospitalization as well as mortality for cardiac arrythmia. These associations showed clear temporal patterns with the strongest effects being observed at the same day (lag 0). With a risk ratio of 1.041 (95% CI, 1.017-1.065) per 1 ppm, CO had the largest impact. Similarly, every 10 ppb increment of NO_2 and SO_2 led to an increased risk with RR=1.036 (95% CI, 1.020-1.053) and RR=1.021 (95% CI, 1.003-1.039), respectively. And for every 10 µg/m^3 increase in PM_{10} and $PM_{2.5}$ a risk increase with RR=1.015 (95% CI, 1.006-1.024) and RR=1.009 (95% CI, 1.004-1.014) was observed. Their meta-analysis included studies from all over the world which allowed them to examine regional differences in risk estimations associated with different concentration levels of air pollution. Generally, the effects of air pollution on the risk of arrythmia were greater in Asia. A plausible explanation for this observation is that average concentrations of PM_{10} and $PM_{2.5}$ were almost two to three times higher in the Asian investigations than in the ones conducted in Europe and North America. In Beijing, for instance,

the average 24h-concentration of $PM_{2.5}$ was 105 µg/m^3, meaning it exceeded the WHO recommendations with 24-h concentrations of $PM_{2.5}$ 25 µg/m^3 by far. Additionally, by analyzing dose-response curves their systematic review provided an important overview about the concentration thresholds at which certain air pollution components are observed to cause adverse health effects. While $PM_{2.5}$ leads to increases in risk of hospitalization or mortality for arrhythmia independently of its concentration level, PM_{10} only seems to have an impact on the risk of arrythmia at levels higher than 30 µg/m^3 (30-50 µg/m^3: RR=1.016 per 10 µg/m^3 , 95% CI, 1.004-1.027; > 50 µg/m^3: RR=1.006 per 10 µg/m^3, 95% CI, 1.004-1.007) (87). Regarding the relationship between different air pollutant levels and the risk for AF, the results of Zhao et al. (2014) and Monrad et al. (2017), on the other hand, demonstrated a linear connection between the levels of PM_{10}, NO_2 and SO_2 and the incidence of AF which indicates a direct proportional link between pollutant levels and increased risk of AF (84). However, a flattening out of the concentration-response curve was observed for NO_2 levels beyond 18 µg/m^3, suggesting that the adverse effects of NO_2 stabilize after reaching a certain threshold (86).

Comparing the susceptibility of different age groups showed that elderly individuals generally seem to be more affected (84). For example, after exposure to $PM_{2.5}$, an effect of up to 5% was observed for study participants of age 75 years and older on the same day (83). This observation may be explained by the prevalence of cardiopulmonary diseases which is generally higher in the elderly. It is probable, that the effects are larger in an already impaired CVS (84,85). In this regard, certain cardiovascular comorbidities appear to be especially relevant effect modifiers. Individuals with diabetes mellitus, for example, had a significantly increased risk of being hospitalized for cardiac arrythmia even 5 days after exposure to elevated PM levels, suggesting that diabetes not only enhances the adverse effects of air pollution, but also prolongs them (85). Apart from diabetes, arterial hypertension also seems to be a plausible effect modifier. In study participants who had been diagnosed with hypertension in advance, higher levels of NO_2 were stronger but not significantly correlated with an increased risk of AF. This association seems plausible, since high BP itself is an important predisposing factor of AF (86). In terms of gender-specific differences, the study results had considerable inconsistencies. Zhao *et al*. (2014) observed a heightened risk of AF

associated with pollution concentrations in Chinese women and suspected physiological, anatomical as well es socioeconomic differences to be the cause of this finding. Whereas Angelo G Solimini and Renzi (2017) found men to be more susceptible to elevated levels of PM_{10} and NO_2. With $PM_{2.5}$, however, also women showed an immediate increase of AF-associated ERVs in their study. Results of Zheng *et al*. (2018) and Monrad *et al*. (2017), conversely, did not demonstrate any differences in susceptibility between women and men, suggesting that the effects of air pollution with regard to AF are not modified by gender.

Several mechanisms that may play a role in the connection between air pollution and heart rhythm disturbances, such as AF, are being discussed. Liao *et al*. (2011) provided important insight into possible underlying pathways by investigating the interference of PM with cardiac electrophysiology. Assessing the ECGs of otherwise healthy, non-smoking individuals demonstrated that higher levels of $PM_{2.5}$ resulted in an extension of PR intervals and in a more complex morphology of P-waves. Changes in these two parameters are associated with impaired atrial depolarization. Therefore, PR duration and P-wave complexity are risk indicators of AF. The effects were observed immediately, ½ - 2 hours, after exposure to $PM_{2.5}$. These results suggest that particulate air pollution might acutely trigger AF by interfering with atrial depolarization visible as aforementioned ECG alterations (89). Song *et al*. (2016), Zheng *et al*., (2018) and Monrad *et al*. (2017) mention further hypotheses behind the correlation of air pollution and the risk of AF. These theories involve cardiac autonomic dysregulation with changes in HRV, systemic inflammation and oxidative stress, which may trigger damage of atrial myofibrils (85,86). Since these underlying processes are not only involved in the pathogenesis of cardiac arrhythmia, but also in other cardiovascular pathologies, they are only mentioned briefly at this point. Details about those studies dealing with the possible mechanisms are discussed in section A.

4.5 Section E: Air Pollution and Heart Failure

As outlined in the introduction, the etiology of heart failure is certainly complex and involves a variety of risk factors. Looking at the correlations between air pollution and various CVDs, described in the other sections, it seems plausible that certain air pollutants indirectly promote heart failure by aggravating the underlying causes of it, such as, for example, arterial hypertension and myocardial ischemia. The

following studies, however, put a special focus on the direct influence of air pollution on the development of HF.

Table 5: Articles dealing with association between air pollution and heart failure

Author	Study Details	Exposure	Results
Shah *et al*. (2013)	systemic review and meta-analysis 4 million events in 35 countries	undisclosed	increased risk of hospitalization for ADHF and HF mortality: • CO (per 1 ppm): **3.52%** (95% CI, 2.52-4.54) • NO_2 (per 10 ppb): **1.70%** (95% CI, 1.25-2.16) • O_3 (per 10 ppb): **0.46%** (95% CI, -0·10- 1.02) • SO_2 (per 10 ppb): **2.36%** (95% CI, 1.35-3.38) • $PM_{2·5}$ (per 10 µg/m^3): **2.12%** (95% CI, 1.42-2.82) • PM_{10} (per 10 µg/m^3): **1.63%** (95% CI, 1.20-2.07)
Li *et al*. (2018)	retrospective study, time-series analysis, 15256 cases, Beijing, China	**short-term**	increased risk of daily hospital admissions for CHF per 10 µg/m^3 $PM_{2.5}$: **0.35%** (95% CI, 0.06-0.64%) increased susceptibility: ≥ 65 years, women
Huynh *et al*. (2018)	retrospective observational study 1246 cases of HF + 3011 cases of subsequent all-cause readmissions Tasmania, Australia	**short-term**	increased risk of HF incidence per 10 µg/m^3 $PM_{2.5}$: RR=**1.29** (95% CI, 1.15-1.42) increased risk of all-cause readmissions per 10 µg/m^3 $PM_{2.5}$: RR=**1.07** (95% CI, 1.02-1.17)
Kim *et al*. (2017)	population-based study N=136094 follow-up: 7 years Seoul, Korea	**long-term**	multivariable-adjusted HR for CHF: CO (per IQR 0.25 ppm): **1.86** (95% CI, 1.56-2.21) NO_2 (per IQR 18.4 ppb): **2.40** (95% CI, 2.02-2.85) O_3 (per IQR 15.9 ppb): **0.64** (95% CI, 0.58-0.71) SO_2 (per IQR 2.54 ppb): **2.00** (95% CI, 1.73-2.32) $PM_{2.5}$ (per 1 µg/m^3): **1.44** (95% CI, 1.29-1.61) $PM_{2.5–10}$ (per 1 µg/m^3): **1.44** (95% CI, 1.29-1.61)
Bai *et al*. (2019)	population-based cohort-study N=5.1 million follow-up: 14 y Ontario, Canada	**long-term**	multivariable-adjusted HR for incident CHF cases: NO_2 (per IQR 13.9 ppb): **1.02** (95% CI, 1.01-1.04) O_3 (per IQR 6.4 ppb): **1.03** (95% CI, 1.02-1.03) O_x (per IQR 3.4 ppb): **1.02** (95% CI, 1.02-1.03) $PM_{2.5}$ (per IQR 3.5 µg/m^3): **1.05** (95% CI, 1.04-1.05)
Sørensen *et al*. (2017)	Danish Diet, Cancer and Health cohort, N=50935 mean follow-up: 13.4 years Copenhagen and Aarhus, Denmark	**long-term**	multivariable-adjusted IRR of hospital admissions for incident HF: 1-year exposure: **1.07** (95% CI, 1.02-1.12) per IQR 6.6 µg/m^3 NO_2 5-year exposure: **1.08** (95% CI, 1.02-1.14) per IQR 7.1 µg/m^3 NO_2 10-year exposure: **1.07** (95% CI, 1.01-1.14) per IQR 7.5 µg/m^3 NO_2

Shah *et al*. (2013) published a systemic review and meta-analysis in which they included 35 studies. Their collected data showed that exposure to gaseous (CO, SO_2, NO_2) and particulate pollutants ($PM_{2.5,}$ PM_{10}) correlates with mortality due to HF as well as with hospitalization for acute decompensated heart failure (ADHF). A clear temporal link between air pollution levels and HF-related incidences was

observed. The strongest effects appeared on the day of exposure (lag 0) with a risk increase of 2.12% (95% CI, 1.42-2.82) per 10 µg/m^3 of $PM_{2·5}$ and 1.63% (95% CI, 1.20-2.07) per 10 µg/m^3 of PM_{10}. However, the majority of publications included in this meta-analysis were carried out in sites with relatively low levels of air pollution. Since only a few studies took place in large cities, the recent study by Li et al. (2018) is of particular importance, for it provided relevant data about the mega-city Beijing where average $PM_{2·5}$ concentrations exceed 100µg/m^3 and the impact of air pollution on overall health is suspected to be much more pronounced (90). In their retrospective study, Li et al. (2018) investigated the acute effects of $PM_{2.5}$ exposure on the incidence of congestive heart failure (CHF). They evaluated the daily number of people who were hospitalized due to CHF. Their results demonstrated a significant association between increased amounts of fine particulate matter and CHF-related hospitalizations. With every 10 µg/m^3 increment in $PM_{2.5}$ the number of daily hospital admissions for CHF rose by 0.35% (95% CI, 0.06-0.64%). The data showed a largely linear relationship (91).
Similar short-term effects between changes in air pollution levels and the incidence of HF were observed by Huynh et al. (2018). Although the study took place in Tasmania, which has a comparatively low median $PM_{2.5}$ concentration of 2.9 µg/m^3 (IQR: 1.8-6.0), their results also demonstrated a significant correlation between $PM_{2.5}$ and new-onset HF-incidence (RR=1.29, 95% CI, 1.15-1.42). The rise in HF-hospitalizations was most marked one day after exposure to elevated $PM_{2.5}$ levels (lag 1) and reached a peak in the coldest, most humid months. Moreover, a $PM_{2.5}$ concentration of 4 µg/m^3 was identified as a potential threshold, since the incidence of HF only began to increase after $PM_{2.5}$ levels had surpassed this value. This finding might account for the detrimental effects of air pollution observed even in countries with relatively low concentration levels. It might also have major implications on future policies regarding air pollution since the current standard in the EU and the USA for $PM_{2.5}$ is 25 µg/m^3 and 12 µg/m^3, thus many times higher than the threshold proposed in this study (80,92).
In recent years, more studies have been published on how long-term exposure to air pollution is related to the incidence of HF. The studies of Kim *et al*., (2017) and Bai *et al*. (2019) are population-based follow-up studies and not only included CHF, but also several other possible CV outcomes. However, for reasons of comparability, only the results regarding CHF will be discussed in this section.

Kim *et al*. (2017) followed 136094 individuals of Seoul, Korea for a median of 7 years. Their findings demonstrated that chronic exposure to particulate and gaseous air pollutants is significantly associated with a higher risk of CHF as well as all other examined CV-events. In their multivariable-adjusted model, exposure to PM resulted in a HR of 1.44 (95% CI, 1.29-1.61) per 1 $\mu g/m^3$ increase in $PM_{2.5}$ and $PM_{2.5–10}$, separately, and an even higher HR for all gaseous pollutants except ozone (see Table 5). According to Kim *et al*. (2017), the attributable risk associated with air pollution is 30.8% for all cardiovascular events together, which makes air pollution an equally powerful predisposing factor for CVD as other well-known risk factors like diabetes, obesity, hypertension and dyslipidemia (81). Another study regarding this topic has only recently been published by Bai *et al.* (2019). Comparing their findings to the ones of Kim *et al*., (2017) is of particular relevance, since the $PM_{2.5}$ 3-year moving average of 9.6 $\mu g/m^3$ in Ontario, Canada deviates substantially from the much higher mean $PM_{2.5}$ concentration of 25.6 $\mu g/m^3$ in Seoul. The large cohort of more than 5 million people consisted of long-term residents of Ontario that were followed between the years of 2001 to 2015. Their multivariable-adjusted analysis revealed an increase in CHF incidence of 5% (95% CI, 4-5%), 2% (95% CI, 1-4%), 3% (95% CI, 2-3%) and 2% (95% CI, 2-3%) for each IQR increase in NO_2, $PM_{2.5}$, O_3 and O_x, respectively. Their results demonstrated a supralinear association between $PM_{2.5}$ levels and CHF. Based on these steep dose-response curves, they argued, similarly to Huynh *et al*. (2018), that the reduction of $PM_{2.5}$ might even be beneficial in countries with generally low levels of air pollutants (93).

Additional information about the adverse effects of the gaseous pollutant NO_2 was provided by Sørensen et al. (2017). Their study design, with an average follow-up of 13.4 years of a Danish cohort, allowed them to examine the relationship between NO_2 levels and the incidence rate ratio (IRR) for HF in a time span of 1-year, 5-year and 10-year exposure, separately. Elevated levels of NO_2 were significantly correlated with an increased risk of HF in all three time-windows. Moreover, in their fully adjusted analysis the IRR for 1-year exposure was 1.07 (95% CI, 1.02-1.12) and remained almost constant in the 5-year and 10-year analysis (see Table 5). This finding suggests that the detrimental effects of NO_2 are significant after one year of exposure, but do not seem to accumulate over time (94).

Several studies investigated the role of sex, age and cardiovascular comorbidities as possible effect modifiers. However, the results are rather conflicting. Bai *et al*. (2019), for example, observed a higher risk of CHF in younger participants, while in the study of Li et al. (2018) people over 65 years of age were more susceptible to the adverse effects of air pollution. Also, Li et al. (2018) reported a higher vulnerability of women, whereas Sørensen *et al*. (2017) found that the relationship between air pollution and HF was stronger in men. They suspected the lifestyle of men involved in their study to be the reason for this finding. It was considered generally unhealthier in terms of diet, physical activity and habits like smoking.
In the same study of Sørensen *et al*. (2017) people with comorbid conditions like hypertension and diabetes had a higher risk of developing air pollution-related HF. Other studies, however, did not observe any difference in risk associated with sex and cardiovascular factors (81,93).
Several possible explanations for the association between air pollution and incidence HF are outlined in the studies. According to Shah *et al*. (2013), air pollution might directly and indirectly increase the demands on the heart, thus causing it to fail, by triggering vasoconstriction, arterial hypertension and arrhythmias. In this context, they also include the findings of other studies linking air pollution to pulmonary vasoconstriction, elevated right ventricular pressure, ventricular remodeling and myocardial fibrosis (90,95,96). In addition, Bai *et al*. (2019) and Huynh *et al*. (2018) discuss the role of systemic inflammation, oxidative stress, autonomic dysfunction and atherosclerosis in the pathophysiological processes behind the relationship of air pollution and heart failure (92,93). In section A these mechanisms are outlined in more detail.

5 Conclusion

There is a rapidly growing body of literature investigating and analyzing the effects of air pollution on the CVS. Associations between exposure to air pollution and CV morbidity and mortality have been well documented. Air pollution has especially been linked to increases in risk of developing hypertension, ACS, MI, cardiac arrhythmia and HF.

Inclusion of studies that were conducted in various geographical regions all over the world, allowed for a comparison of changes in CVD risk associated with different concentration levels of air pollutants. Especially pronounced effects of air pollution have been observed in studies that were conducted in Asian cities, where mean concentration levels of air pollution are substantially elevated (84,85,87). Additionally, analysis of the current literature showed that certain air pollution components, such as $PM_{2.5}$, seem to have particularly harmful effects on the CVS. Some of the most intensively investigated, potential mechanisms that underlie the detrimental effects of air pollution include induction of oxidative stress and systemic inflammation, autonomic imbalance and thrombogenicity.

Some studies demonstrated alarming results showing that adverse effects of air pollution may occur at much lower concentration levels then current air quality guidelines suggest (92). This indicates that the recommended limits are still set too high. Reduction of air pollution through implementation of more rigorous air quality guidelines may potentially lower the incidence of CVDs by eliminating air pollution as a cardiovascular risk factor. More studies investigating the impact of reducing air pollution may provide additional insights regarding this matter.

Many studies have used measurements of fixed-site monitoring stations as a basis of their evaluations. Since the data of environmental monitoring may not reflect the level of individual exposure, future investigations that estimate personal exposure levels more precisely may be needed (60,66,84,86).

Even though it was not a specific focus of this review, a number of studies have implied differences in susceptibility to air pollution depending on age, sex, ethnicity and pre-existing medical conditions. The strongest effect modification was observed with older age (> 60 years), diabetes mellitus and overweight. However, other studies demonstrated that air pollution also endangers the health of young and healthy individuals. In sum, the collected evidence of this review suggests that

air pollution is a global issue affecting the cardiovascular health of individuals of different age groups, sex, health status and ethnicity.

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