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OCCUPATIONAL EXPOSURE TO PARTICLES IN RELATION TO CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND CARDIOVASCULAR DISEASE

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Occupational exposure to particles in relation to chronic obstructive pulmonary disease and cardiovascular disease
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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This thesis is dedicated to my lovely boys, Alfred and Viktor, who are constant reminders of what is important in life, and my husband Markus, for your endless support and love.

POPULAR SCIENCE SUMMARY OF THE THESIS

Working is a big part of our adult everyday life, and for most people necessary to be able to earn an income and thereby afford providing ourselves and families with items needed for living. As the population is aging so is the number of years people are expected to work with people having to work in higher ages. Two of the worlds, and also high-income countries like Sweden's most common diseases, which contribute to poor health and of which people are dying are cardiovascular diseases (CVDs) and chronic obstructive pulmonary disease (COPD), both diseases known to partly be caused by occupational particle exposure. At the same time, in many workplaces the air contains various levels of dust, for example within sectors such as mining and quarrying, construction, and traffic. For some types of dust, the levels have also remained similar in Sweden since 2001, and the proportion of people exposed are similar.

This thesis investigated the relationships between dust exposure at work and being ill in COPD and first having the common CVD myocardial infarction (MI), respectively. We looked into if the risks are different for different types of particles in the dust, and if they differ between men and women. We also investigated if the risks are higher with higher levels of particles in the air. As smoking is the most common cause of COPD, and socio-economy might affect the risk of developing COPD, we considered smoking and education as a proxy for socio-economy in our analyses. Furthermore, as there are multiple causes for having a MI, we adjusted for other occupational exposures (psychosocial, physical workload, noise) as well as for life-style factors of smoking and body-mass index, and for the level of education.
To be able to detect early changes in the body which could end up in CVD, we studied if there were any changes in common biological markers in blood as well as blood pressure and pulse rate when workers were exposed to particles at work. Then we also compared the levels of the markers with levels when the workers had been at vacation.

For COPD, the results show an increased risk among men if they are exposed to any type of inorganic, organic, and high levels to any combustion particles, and more specifically small (respirable) particles of crystalline silica (quartz), gypsum and insulation, diesel engine exhaust, and welding fumes. Among women we found increased risks if they are exposed to various organic particles from animal, flour, leather, plastic, soil, soot, and textile. For all particle types the response was higher with higher levels of exposure.
For first MI, after adjusting for the effect of other occupational exposures, we found increased risks for the whole study population if exposed for several years to different combustion compounds, gases, and metals, as well as to oil mist, benzene, gasoline, pulp or paper dust, and respirable dust. Effects were also seen for welding fumes and quartz dust. Also, for some of these particle types, exposure one year before the infarction there was an association with higher risks if exposed to higher levels.
The studies of early changes in markers support the idea that there are adverse effects in the body after exposure to dust at work. At low to moderate levels of dust, the levels of some

markers for metabolism changed, and resting pulse rate was higher. After vacation blood pressure was reduced and some markers changed. Also, after several years of particle exposure at work, adverse effects were seen. In the short-term, we also saw elevated pulse rate within the same minute after particle exposure. Interestingly, the effect was higher if the worker was simultaneously exposed to noise.

To protects workers from adverse health effects, occupational exposure limits (OELs) are set in different countries by authorities. In the included studies, adverse effects were seen both for COPD and CVD at levels of exposure which were below the current European and Swedish OELs for respirable crystalline silica and respirable dust.

So, what can one as an employer or employee in dusty work environments due? It is not always easy to know how high the levels are. First, you should recognize the problem. If you don't know the levels, other specialties can help you measure, for example occupational health services in Sweden. Then, if possible, you should try to work in such a way that there will be no dust in the air. If not possible, you should try to ventilate the working area or in another way remove dust from your worksite. If that does not help you can enclose the area, machine etc. that is generating the dust so that not so many are affected. One could also let as few people as possible work in these areas and for shorter time-periods, for example by working odd hours or rotating work tasks. Lastly, proper personal protective equipment should be used to avoid inhaling the dust.

To conclude, by improving work environment, for example by reducing occupational exposure to particles, poor health will be prevented. This increases the likelihood of people remaining at work, hence working longer and in higher ages. Reducing particle exposure levels at work would most likely prevent COPD and CVDs.

ABSTRACT

Objective: The working life is expanding with increased retirement ages as the population is aging, in Sweden but in also other parts of the world. However, workers with poor health might not cope with working in higher ages. Two of the world's most common causes of death, chronic obstructive pulmonary disease (COPD) and cardiovascular diseases (CVDs) are partly due to exposures from work. Exposure to particles increase the risk of incident COPD and CVD. However, more research is needed on the effect of occupational exposure of particles of different origin, and to which extent they contribute to COPD and different types of CVD, including dose-response relationships. The overall aim of this thesis was to investigate occupational particle exposure in relation to COPD and CVD, investigate effects of different particle types, dose-response relationships, and potential differences in effects in men and women.

Methods: This thesis comprises four studies, two epidemiological studies, one on COPD and one on CVD resulting in two papers, and two field studies on CVD. **Study I** is a population-based longitudinal study in which we investigated the smoking-adjusted risk of COPD associated with occupational exposure to 13 particles/groups (inorganic, organic, combustion particles, and welding fumes). We formed a cohort of subjects born in 1965 or earlier who responded to the Stockholm Public Health Survey in 2002, 2006, or 2010 with follow-up surveys in 2007, 2010, and 2014, in total 43,641 subjects. Participants were identified as COPD cases if they had been diagnosed with COPD by a physician during 1990-2014 or were prescribed anticholinergic medication specific for COPD. A job exposure matrix (JEM) was used to estimate occupational particle exposure. **Study II and III** investigated the association between particle exposure and markers of CVD. They are based on measurements of respirable silica, respirable dust, and dust of PM 0.1-10, and on biological sampling of included participants within construction industry. Study II, based on 65 participants, investigated if occupational particle exposure is affecting common biomarkers for CVD, both cross-sectionally at work and longitudinally before and after vacation. In study III, based on 46 participants, our aim was to study short-term effects on pulse rate and blood pressure associated with rapid varying particle levels at work, but also intermittent noise. **Study IV** analyzed the association between occupational exposure to 41 different particles and chemicals and first MI adjusted for joint exposures of lack of decision authority, physical workload, noise, and other particles/chemicals. It is based on the Swedish National Cohort on Work and Health (SNOW) and includes all persons who were born between 1930 and 1990 and working in Sweden (6,437,660 subjects), in this study working at any time between 1985-2013. Occupational history was retrieved from the 1980, 1985, and 1990 National censuses and the Occupational register within the Statistic Sweden's Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA). Cases of first MI were identified from the National Patient Register and the National Cause of Death Register. Other registries and cohorts were matched to add additional information of education, smoking, and body mass index (BMI). Four different JEMs were used to estimate the different occupational exposures.

Results: After adjusting for smoking, men occupationally exposed to any type of inorganic, organic, high levels to any combustion particles, and high levels of welding fumes had increased risk of incident COPD. Specifically, respirable crystalline silica (RCS), gypsum and insulation, diesel exhaust, and high levels of welding fumes were associated with COPD and showed dose-response relationships. There was also a tendency of dose-response relationship among men exposed to particles of asphalt/bitumen. For women there was an increased risk of COPD among those highly exposed to various organic particles from animal, flour, leather, plastic, soil, soot, and textile. The population attributable fractions in all ages were 10 % for men and 3 % for women (**study I**).

The two field studies showed changed levels of markers of CVD. Low to moderate occupational exposure to all types of the particles included (median levels: respirable silica 0.015 mg/m^3, respirable dust 0.259 mg/m^3, particulate matter (PM) 0.1-10 0.473 mg/m^3) was associated with higher homocysteine levels, lower high-density lipoprotein-levels, and higher resting pulse rate. Also, long-term (years) occupational exposure to particles was associated with changes in low-density lipoprotein and homocysteine levels (**study II**). Furthermore, PM 0.1-10 in levels above 0.480 mg/m^3 was significantly associated with elevated pulse rate within the same minute. A significant positive association with pulse rate was also found for noise exposure, and there was an additive effect on pulse rate if simultaneously exposed to particles and noise (**study III**).

With regard to first MI, for the whole population of all ages, significant increased risks were observed with cumulative exposure of particles adjusted for joint occupational exposures for the combustion compounds diesel and gasoline engine exhaust, polycyclic aromatic hydrocarbons (PAH) including benzo(a)pyrene (BAP), and sulfur dioxide (SO2), the gases carbon monoxide (CO) and volatile sulfur compounds, and the metals cadmium (Cd), chromium (Cr), iron (Fe) and lead (Pb), as well as for oil mist, benzene, gasoline, pulp or paper dust, and respirable dust. Near significant associations were seen for welding fumes and quartz dust. There were some differences between sexes. Recent exposure was also significantly associated with MI in the whole study population for diesel engine exhaust, PAH including BAP, SO2, CO, volatile sulfur compounds, Cd, Fe, formaldehyde, welding fumes, asbestos, and flour dust, for most exposures with dose-response relationships (**study IV**).

Conclusions: There are several particle types which are associated with COPD and first MI, respectively. Additionally, some particle types show effect on these two outcomes in two or more of the included studies, i.e., diesel engine exhaust, welding fumes, and respirable particles/silica which all are associated with both COPD and MI, even in levels below the OELs for respirable silica, and respirable inorganic particles. Results from the field studies also indicate changes in markers of CVD if occupationally exposed to respirable particles and particles of PM 0.1-10. Preventing poor health by improving work environment, for example by reducing occupational exposure to particles, will increase the likelihood of people remaining longer at work, and would most likely prevent incident COPD and CVD.

LIST OF SCIENTIFIC PAPERS

There are four scientific papers of which this thesis is based. In the text they will be referred to by their Roman numerals I-IV.

I. **Grahn K**, Gustavsson P, Andersson T, Lindén A, Hemmingsson T, Selander J, Wiebert P. *Occupational exposure to particles and increased risk of developing chronic obstructive pulmonary disease (COPD): A population-based cohort study in Stockholm, Sweden*. Environ Res. 2021; doi.org/10.1016/j.envres.2021.111739

II. **Grahn K**, Broberg K, Gustavsson P, Ljungman P, Lindfors P, Sjöström M, Wiebert P, Selander J. *Occupational exposure to particles and biomarkers of cardiovascular disease – during work and after vacation*. Int Archives of Occ and Env Health. 2022; doi.org/10.1007/s00420-022-01900-5

III. **Grahn K**, Vikström M, Broberg K, Ljungman P, Gustavsson P, Lindfors P, Wiebert P, Sjöström M, Selander J. *Short-term variations in occupational exposure to noise and dust and associations with pulse rate and blood pressure* (Submitted manuscript)

IV. **Grahn K**, Lissåker C, Andersson T, Gustavsson P, Wiebert P, Alfredsson L, Ljungman P, Broberg K, Albin M, Selander J. *Occupational exposure to chemicals and particles and incidence of myocardial infarction – a nationwide cohort study in Sweden* (Manuscript)

SCIENTIFIC PAPERS NOT INCLUDED IN THE THESIS

I. Broberg K, Svensson J, **Grahn K**, Assarsson E, Åberg M, Selander J, Enroth S. *Evaluation of 92 cardiovascular proteins in dried blood spots collected under field-conditions*. BioEssays. 2021; 43:2000299; doi.org/10.1002/bies.202000299

II Gliga AR, **Grahn K**, Gustavsson P, Ljungman P, Albin M, Selander J, Broberg K. *Short and long-term associations between serum proteins linked to cardiovascular disease and particle exposure among constructions workers*. Scand J Work Environ Health. 2022; doi:10.5271/sjweh.4071

CONTENTS

LIST OF ABBREVIATIONS

A_1AT	Alpha-1-antitrypsin
ACGIH	American conference of governmental industrial hygienists
ALHC	Aliphatic/alicyclic hydrocarbon solvents
ANS	Autonomic nervous system
ARHC	Aromatic hydrocarbon solvents
ATC	Anatomic therapeutic chemical
BAP	Benzo(a)pyrene
BMI	Body mass index
BPM	Beats per minute
Cd	Cadmium
CI	Confidence interval
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
Cr	Chromium
CRP	C-reactive protein
CVD	Cardiovascular disease
DALY	Disability-adjusted life year
ECHA	European chemicals agency
Fe	Iron
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GOLD	Global initiative for chronic obstructive pulmonary disease
HDL	High-density lipoprotein
HR	Hazard ratio
ILO	International Labour Organization
ISCO	International standard classification of occupations
JEM	Job exposure matrix
LDL	Low-density lipoprotein
MFR	Medical birth register (*Medicinska födelseregistret*)
MI	Myocardial infarction

NCD	Noncommunicable disease
Ni	Nickel
OEL	Occupational exposure limit
PAF	Population attributable fraction
PAH	Polycyclic aromatic hydrocarbons
Pb	Lead
PCB	Polychlorinated biphenyls
PM	Particulate matter
RCS	Respirable crystalline silica
SAA	Serum amyloid-A
SO2	Sulphur dioxide
TLV	Threshold limit value
WHO	World Health Organization

1 INTRODUCTION

In 2019, at global level 3.2 million deaths were due to COPD (1) and 18.9 million due to CVDs (2). CVDs with ischemic heart disease were the first and stroke the second two most common causes of death, accounting for one-third of all deaths globally, and COPD the third most common cause of death (3). In 2013, the World Health Organization (WHO) Member States agreed on global mechanisms to reduce the avoidable noncommunicable diseases (NCD)-burden including a "Global action plan for the prevention and control of NCDs 2013-2020". The aim of this plan is to reduce the number of premature deaths from NCDs including COPD and CVD by 25% by 2025. This will be done through nine voluntary global targets (4). In industrialized countries like Sweden, occupational particle exposure is of importance and contributes to NCDs such as circulatory and respiratory system diseases (5). Therefore, reducing occupational particle exposure is one tool for achieving the WHO-plan. Also, occupational particle exposure is common in various sectors with many persons exposed at work. Furthermore, the occupational exposure levels are generally higher than in ambient air, especially in high income countries like Sweden. As occupational particle exposure is common, and CVDs and COPD also are common it is important to study occupational particle exposure and its relation to these health outcomes. Furthermore, in high-income countries like Sweden, the population is ageing. This leads to the working life expanding. However, for workers with poor health, new regulations with changes in the pension system, for example with higher retirement ages, this may be troublesome as they might not cope with working in higher ages.

The core aim of this thesis is to investigate the association between occupational exposure to particles and COPD and CVD. This was done in two different ways, through two epidemiological studies, one on COPD and one on CVD resulting in two papers, and through a field study on CVD resulting in two papers. The focus in this thesis is Sweden, however both occupational particle exposure and COPD and CVD are of global concern. In this book the background to the area and its knowledge gaps, and thereby the four papers, is first introduced. Then follows the aims, material and methods, results, discussion, and some conclusions of the four papers. These papers (two peer-reviewed articles and two manuscripts) are found in this thesis.

2 LITERATURE REVIEW

We are all exposed to airborne particles in our daily life in the outdoor environment, in our homes and at our work. Particles are present in air pollution from traffic, burning of biomass, and other sources, and consists of chemical, physical and biological agents (6). Air pollution is the dominating source of environmental pollution in the world today and the largest environmental health risk in the world with ambient (outdoor) air pollution killing around 3 million people every year (WHO 2016) (7).

Within ambient air, particulate matter (PM) is usually separated in different size ranges for monitoring purposes. The fractions being particles with a size of 2.5-10 µm called the coarse fraction (PM10), particles with a size of 0.1-2.5 µm called the fine fraction (PM2.5) and a size 0.1 µm or less called the ultrafine fraction (UFP) (8). The content of air pollution in occupational settings differ from the outdoor air. At work sites there are many inorganic and organic particles which are coarse particles (PM10), but there are also finer fractions (9). The particle size fractions used for monitoring in occupational settings also differ and often uses the categories inhalable (fraction we inhale through nose and mouth), thoracic (the fraction of the inhaled particles which passes the larynx), or respirable (fraction that penetrates the alveolar region of the lung) (10).

2.1 OCCUPATIONAL EXPOSURE TO PARTICLES

In 2012 Takala et al estimated that around 2.3 million deaths globally each year are due to work, with the majority, 2.0 million being due to work-related diseases. Occupational particle exposure contributes to diseases such as cancer, circulatory and respiratory system diseases. Especially in industrialized countries, where infectious diseases are low compared to countries not that well developed (5).

Exposure to particles is common in occupations in for example construction industry, transport and communications sector, mining, quarrying, petroleum extraction, agricultural sector, production of various types, and cleaning. Therefore, authorities and organizations around the world provide occupational exposure limits (OELs) in order to prevent workers from hazardous exposure. For example, the American Conference of Governmental Industrial Hygienists (ACGIH) is a scientific organization within industrial and occupational hygiene. The organization put forward a number of threshold limit values (TLVs) of different agents. The TLVs are based on published and peer-reviewed literature which are reviewed by scientific committees. No economical or technical factors are considered. The TLVs are not binding and represent exposure levels which are safe and do not entail any risk of disease or injury in workplaces.
Within the European Union, the European Chemicals Agency (ECHA) evaluate health-aspects at independent scientific committees. The European Union then agrees on occupational exposure limits (OELs) for different agents. The OELs are based on health,

economy and technical factors and can be either binding or indicative. Each member state can choose to implement the European OEL in its national provisions but not a higher value. A lower value is accepted. In Sweden we have the Swedish Work Environment Authority which produce provisions within the field of work environment. One of the provisions is Hygieniska gränsvärden, which provides a list of OELs of airborne occupational pollutions (10). The list is based on the European OEL. In Sweden, more than 500 substances have limit values.

Over time, the occupational particle exposure levels have changed in Sweden. Though, there are some levels that have not changed much for the last decades, for example the exposure levels of respirable crystalline silica (RCS) and welding fumes which have not changed much since 1990. However, the levels of diesel engine exhaust have decreased since 1990 and the levels of wood dust have remained similar since 2001 (11).

As discussed above, TLVs/OELs is at whole or partly based on scientific knowledge. However, more research is needed to establish if the OELs really protects workers. As the levels of pollutions generally are higher in occupational settings than in ambient air, especially in high income countries, and many persons are exposed at work at similar levels for the last decades for some particle exposures it is important to study occupational exposure and its relation to different health outcomes.

2.2 COPD

COPD is a common disease. Globally, WHO has estimated that in 2019, COPD was the third most frequent cause of death overall, and in high income countries it was the fifth cause (3). At global level 3.2 million deaths and 74.4 million disability-adjusted life years (DALYs) were due to COPD in 2019 (12). According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD)-report of 2023 the burden and prevalence of COPD is expected to increase due to an aging population and continuing exposure to various risk factors for COPD (13).

The costs of the disease are very high. The GOLD-report of 2023 states that the total direct costs for COPD within the European Union is 38.6 billion Euros per year. In the United States the costs are expected to increase to 40 billion Dollars per year. The more severe disease, the more costly (13).

COPD has a slow progression, and many patients get their diagnosis in a late, severe state. According to GOLD-criteria, an airflow limitation which is not fully reversible and increases over time characterizes the disease. The definition of COPD is mainly based on spirometry results as $FEV_1/FVC < 0.7$, i.e., the ratio of the vital capacity the first second of forced expiration (FEV_1) and the full forced vital capacity (FVC) being less than 70 %. However, an associated history of exposure is required according to the criteria, often many years of smoking tobacco or exposure to other toxic particles and gases (13). In the airways, archetype

inflammatory changes can be found which may lead to structural changes. Limitation of the airflow caused by bronchiolitis is a fundamental finding (14).

One of the few known causes of COPD is deficiency of alpha-1-anti-trypsin (A_1AT), although this is a rare condition and the population attributable fraction is low, about 1 % (15). The most important risk factor is tobacco-smoking (13, 16). According to a review from 2010, smoking was at global level associated with 54 % of COPD-deaths among men and with 24 % among women, both groups aged 30-69 years. In industrialized countries the fractions were higher than those in developing countries, 84 % compared to 49 % for men, and 62 % compared to 20 % for women (6).

Socioeconomic status and COPD has also been studied. According to a study presented in 2009, COPD-cases and referents were comparable regarding the confounding factors age, sex, and race. However, educational level and annual household income were significantly lower for those with COPD. One should however keep in mind that this was when comparing with matching referents, and not the general population. The study furthermore indicated that the risk of COPD markedly increased (odds ratio (OR) 14.1, 95 % confidence interval (CI) 9.33-21.2) with joint exposure to both smoking and occupational factors (17).
In another study COPD-cases´ occupation and education in relation to socioeconomic status and health-related quality of life was investigated. Patients who belonged to the unskilled professional groups and with lower level of education had a poorer health-related quality of life. Even if patients did not have to pay to visit health care services and all patients could do so, low socioeconomic position was associated with a higher risk for COPD (18). There are also other studies which support that COPD is associated with poor quality of life and low income (19, 20).

2.2.1 Occupational exposure to particles and COPD

In 2021 the International Labor Organization (ILO) considered dusts in occupational settings to possibly contribute to COPD (21). Both systematic analyses and reviews within this field using different methods in different types of populations and occupational settings also suggest that occupational exposures and COPD are causally associated. An estimation is that around 15 % of COPD is due to exposures at work (22-24). A systematic review that assessed population-based studies using Job Exposure Matrices (JEMs) for calculating smoking-adjusted risk of COPD in relation to occupational exposures was published in 2016. The study concluded that even at low levels of occupational mineral dust-exposure there was an increased risk of COPD. The risk was also elevated when subjects were exposed to high levels of gases and fumes (14). According to another review (2012) there are some specific agents which might elevate the risk of COPD, for example silica dust, coal mine dust, agricultural and textile dust, as well as welding and cadmium fumes (25). Furthermore, in a systematic literature review from 2014, the authors concluded that occupational industrial inorganic/mineral exposure (welding, coke, coal, asphalt, silica, tunnel work, cadmium, glass

bangle work, bleach work) and organic exposure (flax, jute, farming, grain, wood, rubber, endotoxin) were associated with COPD. Though, the review found no significant associations between cement dust exposure and COPD or between cotton dust and low FEV_1 (26).

Other studies have found elevated risks of COPD among persons being occupational exposed to particles. An American case control-study (2015) of elderly construction workers found an increased risk of COPD associated with occupational exposures to welding fumes and silica dust, and associations with asbestos and cement dust. Also, subjects exposed to metal cutting and grinding aerosols, isocyanates, engine exhausts, acids/caustics, organic solvents, molds/spores and wood dust had an elevated risk for COPD (27). Welding fumes was also associated with an excess risk of COPD in a study (2015) of Korean shipyard welders with an OR of 3.9 (95 % CI 1.4-13.3) in the group which was middle exposed and an OR of 3.8 (95 % CI 1.03-16.2) in the group which was high exposed when compared to the low exposed group (28).
A Swedish cohort-study (2004) followed more than 300,000 construction workers for a period of 28 years (1971-1999). Exposure to any airborne compound resulted in an increased mortality of COPD with a relative risk (RR) of 1.12 (95 % CI 1.03-1.22). There was also an association between inorganic dust and COPD-mortality with a hazard ratio (HR) of 1.10 (95 % CI 1.06-1.14). Among never-smokers the corresponding figure was even higher (HR 2.3, 95 % CI 1.07-4.96). Their estimated fraction of COPD due to any airborne occupational exposure was 10.7 % for the whole studied population and 52.6 % for those who never had smoked (29).

A systematic review of COPD in farmers (2017) concluded that the work tasks involved in farming were related with an excess risk of COPD-incidence. Though, the risk could differ depending on type of farm. In the review, livestock farmers were found to be at higher risk compared to crop farmers. Also, several variables influence the disease prevalence, such as dusts, chemicals, gases, and infectious agents. Furthermore, greenhouses may have higher exposure to biological and chemical dusts due to their confined spaces (30).

Some other occupations have also been associated with elevated risks of COPD. In the population-based cohort-study of the UK Biobank (2016) high risk occupations were calculated using prevalence ratios (PR) with 95 % CI. Some examples are seafarers (PR= 2.64, CI 1.59-4.38), coal mine operatives (PR=2.30, CI 1.00-5.31) and cleaners (industrial: PR=1.96, CI 1.16-3.31, domestic: PR=1.43, CI 1.28-1.59) (31).

A systematic review and meta-analysis from 2017 of organic dusts (cotton, grain, farming, paper, and wood dust) found indications that exposure to organic dust entail an accelerated decline of lung function. Though, there was no consistency in the included studies of which organic particles that were the most harmful. Furthermore, only a few of the studies included in the systematic review explored effect modification by sex (32).

Overall, very few studies analyse the risk of COPD in each sex in relation to different types of dust.

2.2.2 Biological mechanisms for particle-induced COPD

COPD is a disease which involves both large and small airways and the alveoli involved in gas transfer. Several pathological pathways are thought to be engaged in the process. The inhalation of toxic particles and gases are thought to be central (33). However, the pathophysiological mechanisms that link inflammation with loss in FEV_1 are not fully understood. Factors other than toxic and irritant inhalation may also be important. For example, underlying genetic susceptibility and the regulation of the immune system may play a role. Also, mechanisms which are involved in repair of cells and decreasing and ending inflammations may also be of importance (34).

Many inhaled gases, fumes and irritant dusts activate macrophages and leukocytes in the alveoli. This will in turn lead to the release of reactive oxygen species, which may cause inflammation in the airways and lungs (14). Local inflammatory processes may lead to chronic bronchitis (inflammation in the airways), small airways disease, and emphysema (damaged alveoli). Consequences on the long-term are pulmonary hypertension and systemic inflammation (35).

Different types of exposures are related to COPD, and it is unknown if they all follow the same pathway, or if different pathways end in the same result (COPD). One example is among workers exposed to organic dust, where endotoxin may be a cause of respiratory disease. Endotoxins is one building part of the outer membrane of Gram-negative bacteria. It is potent in the inflammatory process when compared to other microbial components of organic dust. This could lead to inflammation (36).

One way of studying mechanisms is to study early and late changes of markers in the body (biomarkers).

2.2.3 Markers of COPD

2.2.3.1 Biomarkers

A biological marker (biomarker) can be defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention” (37, 38). Preferable, the biomarker should be measured fast and easy. It should be precise and accurate and just measuring what is of interest. The biomarker should also have a small variation for the same individual (39). Traditionally, they can be grouped according to three types of uses, that is screening for risk, diagnostic, and prognostic uses. Biomarkers can also be clustered depending on how they reflect the pathological process.

As COPD is a heterogenous disease with respect to inflammation and etiology, and as there are potentially several pathological pathways which all lead to the single endpoint limited airflow, there is no “universal” biomarker. However, when looking into exacerbations of the

disease, one study (2011) investigated different clinical phenotypes of COPD-exacerbation related to bacteria, virus, or eosinophilic airway inflammation. The corresponding biomarkers of these phenotypes were identified as sputum IL-1β, serum CXCL10 and percentage sputum peripheral eosinophil count (40).

2.2.3.2 Bioimaging markers

It is difficult to find early biomarkers of diseases in the lung since it often is very difficult to collect samples. Measuring markers in blood has its limitations as it will be a proxy for the lung. Another marker is bioimaging technic. One example is a study from 2012 where the group used a parametric response map, a technique which uses voxel-wise images, and used it on whole-lung computed tomography (CT) scans. They thereby identified how much of the small airways that were affected by a disease, and also if there was emphysema. In this sense it is a bioimaging marker which may diagnose the extent of the disease and the phenotype, as well as distribution and location (41). Bioimaging technics has an advantage as they measure changes in the lung directly, but one can discuss if the technic is sensitive enough for early changes.

2.3 CVD

Cardiovascular diseases (CVDs) is a group of several diseases. Most CVDs are related to atherosclerosis, which is when the vessel walls are affected by a systemic inflammation causing a reduced blood circulation and oxygen-shortage in the tissue (ischemia). Coronary heart disease (CHD), which can also be referred to as coronary artery disease (CAD) or ischemic heart disease (IHD), is one major group including myocardial infarction (MI). Cerebrovascular diseases is another major group which includes stroke. Stroke could be ischemic or haemorrhagic (caused by bleeding). However, some conditions are not that well associated with atherosclerosis. Examples are cardiomyopathy (disease in the heart muscle) and cardiac arrythmia (irregular heart rate) (42). Furthermore, CVDs have an impact on other parts in the body such as the lungs, kidneys, brain, and tissue which is peripheral (43).

CVDs are very common. In 2019, CVDs were the most common causes of death, accounting for one-third of all deaths globally (2, 3). IHD followed by stroke were the most common underlying diseases. The number of estimated prevalent cases were in 2019 523 million globally with 18.9 million deaths (2). Within the European Union only, CVDs are the most common causes of death. In 2015, the diseases were estimated to cost 210 billion Euro every year. Of these 53% (111 billion Euro) were related to costs of healthcare, 26% (54 billion Euro) to losses in production, and 21% (45 billion Euro) to the unpaid care of people with CVDs provided by others (44).

There are some established personal risk factors for CVDs. Some of them are non-modifiable such as increasing age and a family history of CVD. Others are modifiable, for example physical inactivity, high alcohol consumption, smoking, and an unhealthy diet (45). The

presence of diabetes, obesity, hypertension, and dyslipidaemia (very high levels of lipids in the blood) are also all established risk factors (45, 46). Furthermore, there are clear associations between psychosocial stress (47-49) and socioeconomic position (50) and several CVDs. However, differences in socioeconomic groups may partly be described by differences in modifiable factors, factors which also reflects in the diseases mentioned above. Furthermore, occupational exposures such as physically strenuous work (51) and noise (52, 53) are risk factors for CVDs.

2.3.1 Occupational exposure to particles and CVD

In a review of epidemiological literature on chemical occupational exposures and CVDs from 2017, a number of chemicals including particle exposures were associated with an increased risk of CVDs. Examples of types of particles being asbestos, arsenic, lead, metal working fluids, and particles from environmental tobacco smoke, as well as crystalline silica, particles from engine exhaust, and welding fumes (54). The latter three are discussed more in detail below. Overall, there are few studies on women and occupational particle exposure in relation to CVDs. Furthermore, joint exposure to other occupational exposures including other particles is seldom studied, as is an interaction with psychosocial exposure and the association between occupational exposure and CVDs in higher working ages.

Respirable crystalline silica

Occupational exposure to respirable crystalline silica (RCS) is very common. Within the European Union 5.5 million workers are regularly exposed (2019), for example within foundry, mining and construction industry (42). A systematic review of epidemiological studies from 2017 (SBU-review) concluded that there is limited evidence of IHD, moderate evidence of pulmonary heart disease, and insufficient evidence of stroke in relation to occupational exposure to RCS (54). Another review from 2019 indicated that even in low exposure intensities of RCS (< 0.05 mg/m^3) the risk for MI is increased. Excess risk of death due to MI was also reported at low cumulative doses (0.9-2.5 mg/m^3-ys) (42). Cumulative exposure to RCS less or equal to 0.1 mg/m^3, has also been positively associated with a linear dose-response relationship with IHD in a study from 2014 (55). However, a study from 2015 showed no dose-response relationship with IHD (56). Liu et al further observed dose-response associations for pulmonary heart disease (55, 57). No increased risk of cerebrovascular disease was noted and no dose-response relationships (57, 58). Furthermore, no dose-response associations were found for stroke (56).

There are very few studies on gender differences since there are few studies on women´s occupational exposure to RCS. Wiebert et al found some differences in dose-response associations between RCS and MI in a study from 2012 (59), and with women being more sensitive to RCS than men in another study from 2022 (60). However, more studies are needed on occupational exposure to RCS in association to different CVD and different gender as well as dose-response relationships.

Engine exhaust including particulate matter

Exposure to diesel engine exhaust is present in many occupations, for example tunnel constructions workers, miners, and professional drivers. In Europe, more than 3.6 billion workers were occupationally exposed to diesel engine exhaust in 2017 (61). Exhaust from diesel-fuelled motor vehicles consists of various gases and particles. The latter being elemental carbon (EC), organic compounds (such as polycyclic aromatic hydrocarbons (PAHs), aromatic, and aldehydes), sulphates, nitrates, and traces of metals and other elements (61).

Related to motor exhaust (both diesel- and petrol fuelled) the SBU-review from 2017 found a moderately strong evidence of heart disease. Furthermore, limited evidence of stroke and hypertension was found (54). Costello et al (2018) indicated an increased risk of IHD due to exposure of respirable elemental carbon and dust. The former is a key agent indicating diesel exhaust (62). A report from 2019 concludes that studies indicate dose-response relationships between diesel motor exhaust and negative cardiovascular effects. Though, more research is needed on detailed exposure data and individual information on confounders, but also dose-response relationships (42).

Welding fumes

In the welding process different respirable particles are generated. Common exposures are small metal and non-metal particles, but also different gases contributes in the exposure (63). The primary particles often agglomerates (64).

The systematic SBU-review on epidemiological studies from 2017 concluded that there is limited evidence for an association with IHD and insufficient evidence for an association with stroke (54). A meta-analysis from 2015 supports a significantly increased risk for acute MI with welding fumes. However, the evidence on other IHD in relation to occupational metal welding fumes and specific welding characteristics/particles are limited (65). A report from 2019 also highlights a need for studies on welding fumes including dose-response relationships (42).

Other particles and chemicals

The epidemiological systematic literature review from 2017 concluded that for heart disease there is moderately strong evidence in relation to exposure to asbestos, limited evidence for arsenic, benzo(a)pyrene (BAP), lead, electrolytic aluminium-production, carbon monoxide (CO,) RCS, production of paper using the sulphate-method, cutting fluids/oil mist, and occupational environmental tobacco smoke. Less and insufficient evidence were found in relation to exposure to asphalt, solvents, production of paper using the sulphite-method, cadmium, mineral dust, organic dust/endotoxins, unspecific metal exposure, and sulphur dioxide (SO2) (54). However, there are several particles/chemicals not sufficiently studied in relation to CVD.

2.3.1.1 Biological mechanisms for particle-induced CVD

Biological mechanisms for CVDs due to particulate matter have been studied. Many of the exposures will probably cause inflammatory processes and atherosclerosis, and in turn lead to an increased risk of CVDs (42). At molecular level, oxidative stress is a critical cause. Oxidative stress is when there are higher levels than normal of free radicals or reactive oxygen/nitrogen species which attack proteins, lipids, and DNA, and harm those. Then, an inflammatory response will also occur.

At integrated, physiological level, three pathways have been suggested after inhaling particles. The first is a systemic inflammatory response as mentioned above. For example, Fang et al suggests that systemic inflammation is a potential mechanism for IHD due to particles (66). A second pathway is imbalance in the autonomic nervous system (ANS) or heart rhythm due to particles interacting with receptors in the lung or nerves, thus leading to rapid changes in pulse rate and blood pressure. The third pathway is particles being transmitted from the lungs into the blood which affects the cardiovascular tissue negatively (67). All three pathways could lead to vascular and blood changes. However, the composition of particles, their sizes, and chemical characteristics, may activate different pathways (68).

2.3.1.2 Biological mechanisms for noise exposure

Two pathways have been suggested for incidence of CVD in relation to noise exposure. The first, direct pathway, is an interaction between the central auditory system and other central nervous system regions. The second, indirect pathway, is activation of cortical. The two pathways may start responses to physiological stress. These involve activation of the two axis' hypothalamus-pituitary-adrenal (HPA), and sympathetic-adrenal-medulla, which leads to elevated levels of stress hormones, but also pulse rate (69). Exposure to noise for a long time may also lead to allostatic load (imbalance in homeostasis) causing increased levels of blood lipids, viscosity, and glucose. Eventually, these changes may lead to hypertension, arteriosclerosis, and then MI and stroke (52).

2.3.2 Markers of increased risk of CVD

2.3.2.1 Biomarkers

There are a number of biomarkers for risk of developing CVDs. The biomarkers can be grouped in different ways, for example based on if they represent a disease specificity, or the pathologic process. Some examples of the latter, which also are used in experimental and epidemiological studies and are indicating early, or late changes related to CVDs, are mentioned here. The acute-phase C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNFA) are used for detection of acute phase response and/or inflammation. Another biomarker of inflammation is serum amyloid A (SAA). F_2-Isoprostanes are reported as authentic and reliable indicators of oxidative stress (70). Another biomarker of inflammation but also coagulation is fibrinogen (39). Fibrinogen, CRP, and

SAA are all CVD-markers which are established (71-73), as are metabolic biomarkers of low-density lipoprotein (LDL), serum high-density lipoprotein (HDL), triglycerides, overall cholesterol, homocysteine, lipoprotein (a) and ApoB100 (39).

Biomarkers have been used in previous studies of particle exposure and CVDs. Westberg et al (2016) found dose-response relationships of IL-6 with particles at occupational settings from welding, cutting, grinding, and other foundry operations (74). In another study of Westberg et al (2019) biomarkers of CVDs in relation to occupational exposure to RCS and other fractions of dust were investigated. Statistically significant increased levels of SAA (particulate fractions of inhalable dust, PM 2.5, and PM 1.0) and fibrinogen (particle number concentration) were observed in the studies´ highest exposure groups. However, no significant elevated levels of IL-6 and SAA were found in relation to exposure of RCS (75). Arant et al (2009) found that a combination of several biomarkers, including IL-6, CRP and SAA, was associated with adverse cardiovascular events (ischemia) among women in the general population (76). In animals that developed plaque in the aorta, SAA was a related biomarker of the formation. Therefore, SAA may play a role in atherosclerosis (77).

2.3.2.2 Other markers

An elevated blood pressure is a pathway to CVD (46, 78), and earlier studies have shown an association between exposure to particles and blood pressure (79, 80). Furthermore, a sustained high resting pulse rate is a risk factor for cardiovascular disease (81). There are indications that if pulse rate is being elevated for longer time periods it will take part in the pathogenesis of vascular disease, and that there is a correlation with inflammatory markers (82).

2.4 KNOWLEDGE GAP

As discussed above several studies including systematic reviews conclude that there is an association between exposure to dust, gas, vapour, and fumes and COPD, even after adjustment for smoking. Associations between particles of different origin and CVDs are also observed in other reviews. However, more research is needed on the effect of occupational exposure of particles of different origin, and to which extent they contribute to COPD and different types of CVDs, including dose-response relationships. Little is also done on occupational particle exposure among women and its relation to COPD and CVDs. Are there safe levels of exposure for different particle types in relation to COPD and CVDs? Do the levels differ between men and women? Furthermore, more research is needed on occupational exposure to particles and early markers of CVDs.

3 RESEARCH AIMS

The overall aim of this thesis was to investigate occupational particle exposure in relation to COPD and CVD, investigate effects of different particle types, dose-response relationships, and potential differences in effects in men and women.

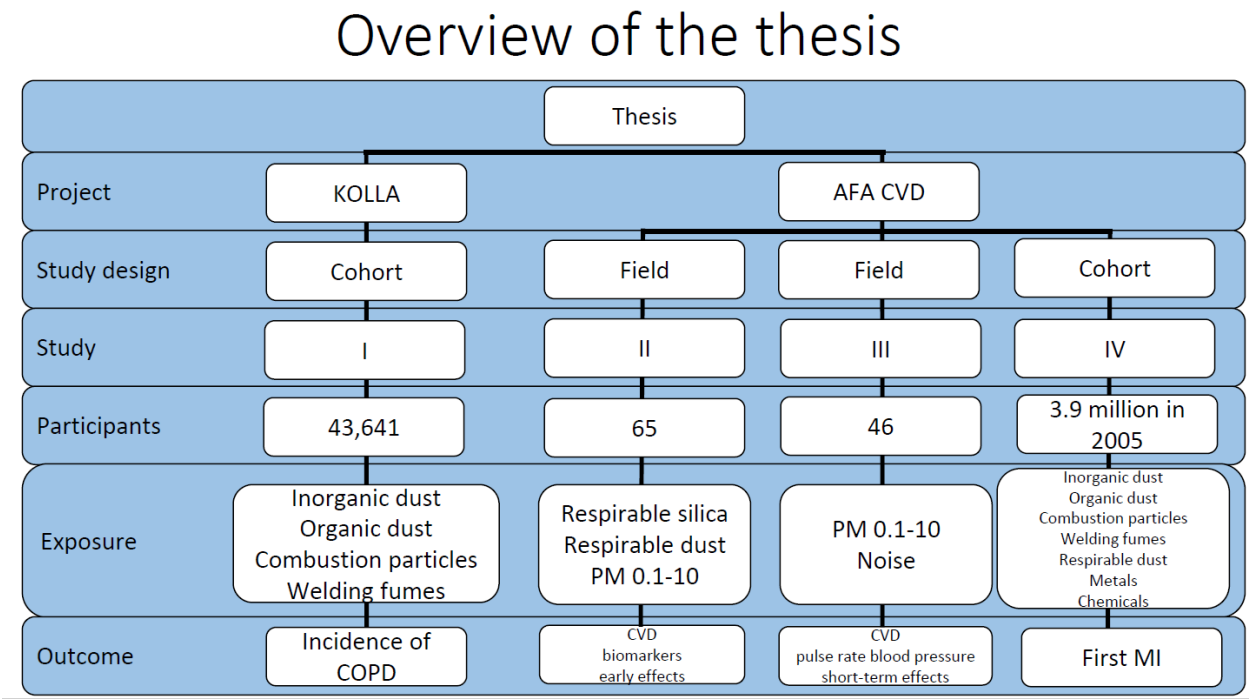
Specific research questions:

- Are there associations including dose-response relationships between exposure to different types of particles (inorganic, organic, combustion, welding) and COPD among men and women?
- If so, are there differences in associations between occupational particle exposure and COPD between men and women?
- Is there an association between exposure to particles and markers for the risk of CVD (blood pressure, pulse rate, inflammation, metabolism, coagulation)?
- Are there associations including dose-response relationships between exposure to different types of particles, separately and with joint occupational exposures, and MI?
- If so, are there differences in associations between occupational particle exposure and MI between men and women?

4 MATERIALS AND METHODS

The thesis consists of two projects which focus on occupational exposure to particles: Particles and COPD (KOLLA) and Particles and CVD (AFA CVD), respectively. Paper I is based on KOLLA, and Paper II - IV on AFA CVD, see an overview in Figure 1.

***Figure 1**. Overview of study design, number of participants, exposures, and outcomes in the included studies*



4.1 COPD STUDY

In this study we wanted to investigate which types of occupational airborne particle exposures that are associated with COPD incidence in men and women separately, and after adjustment for smoking.

4.1.1 Study design

The COPD study design is a population-based longitudinal study. We formed a cohort of subjects who responded the Stockholm Public Health Survey in 2002, 2006, or 2010 with follow-up surveys in 2007, 2010, and 2014.

4.1.2 Study participants

As it requires decades of occupational exposure to particles before developing COPD, only subjects born in 1965 or earlier were included in the cohort. Participants were identified as COPD cases if they were prescribed anticholinergic medication specific for COPD at the time period 2005-2011. Also, information about COPD was derived from the surveys from 2006 and onwards which all included questions on COPD, i.e., if the respondent had been diagnosed with COPD by a physician during 1990-2014, and if so, which year. As some cases were present in both sources, the earliest date information was used in the analyses. Those with a self-reported COPD diagnosis before 1990 were excluded. Furthermore, as smoking is highly associated with COPD, we excluded those with missing data on smoking.

4.1.3 Register-based information / Data collection

For this study, information from several registers were utilized. The surveys described above also all included questions on lifetime history of cigarette smoking. Data on anticholinergic medication was obtained from the National Prescribed Drug Register, and occupational information for each subject from the nation-wide Population and housing census in 1990. If the 1990 census was missing occupational data, we used data from the previous one in 1985. The national Statistic Sweden's Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA) provided information on each subject's educational level in 1990, and the national Cause of Death Register at Statistics Sweden on mortality for the years 2002-2014. We used the Swedish residents' civil registration number to link all the individual data to the cohort. For an overview of the data collection, see Figure 2.

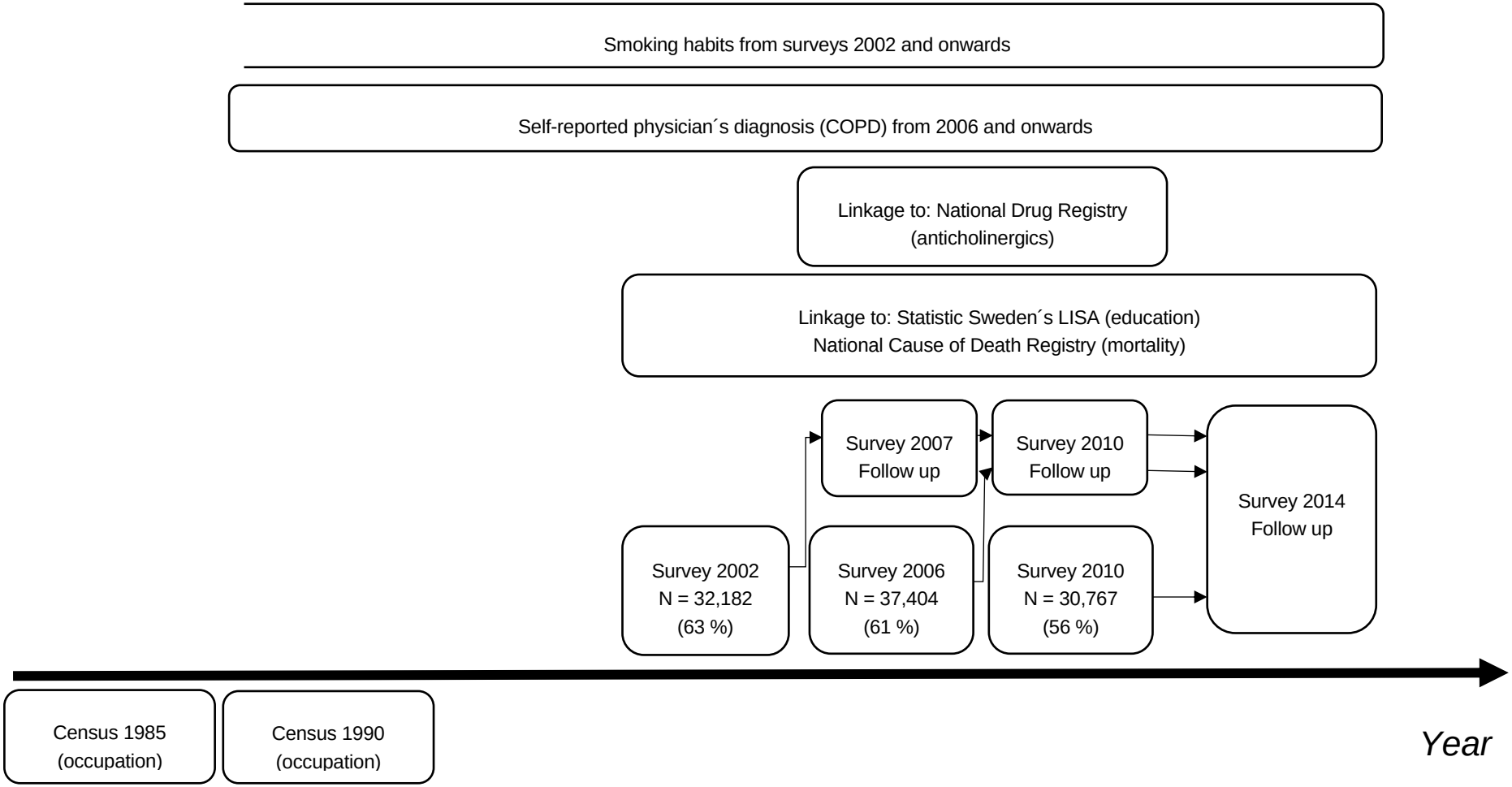


Figure 2*. Data collection of the COPD study* Figure originally published in Supplementary material to: Grahn K, Gustavsson P, Andersson T, Lindén A, Hemmingsson T, Selander J, Wiebert P (2021) *Occupational exposure to particles and increased risk of developing chronic obstructive pulmonary disease (COPD): A population-based cohort study in Stockholm, Sweden*, Environmental Research, doi.org/10.1016/j.envres.2021.111739 and is licensed under a Creative Commons Attribution (http://creativecommons.org/licenses/by/4.0/)

4.1.4 Exposure assessment and job exposure matrix

Each study participant's occupation in 1990 (or 1985 if data was missing in 1990) was coded according to the job classification scheme FoB90 (Population and housing census) on a 3-digit level, which is based on the Swedish version of International Standard Classifications of Occupations (ISCO) 58. To assess exposure, we then linked each subject's occupational title with the corresponding 3-digit code to a job exposure matrix (JEM). The JEM we used is based on the Finnish FINJEM but adapted to conditions in Sweden and holds information on exposure prevalences and levels for approximately 300 Swedish labor market occupations for the period 1985-1994. The exposure levels are based on measurements from Sweden, and if not available from other Nordic countries.

Particles of interest in this study that were available in the JEM were; inorganic particles including RCS, iron dust, other inorganic particles and fibres (gypsum and insulation material), organic particles including wood dust, paper dust, oil mist, cooking fumes, other organic particles (particles from soil, leather, plastic, soot, animal, textile, flour), combustion particles including asphalt/bitumen particles, diesel exhaust, PAH, other combustion particles (particles from environmental tobacco smoke, plastic smoke, fire smoke) and welding fumes.

4.1.5 Statistical analyses

Confounding variables for the study was based on knowledge from literature and statistical analyses. Confounding risk factors included in the models were age and smoking status, and in some analyses also education. Smoking status was dichotomized as ever vs never smoking and number of pack-years among the ever-smokers was stated. Education was divided in three groups of highest achieved level in 1990 (pre-secondary, secondary, post-secondary school). However, education is closely correlated with occupation, and including education may lead to an over-adjustment.

Separate for men and women, a discrete time proportional hazards model was used to estimate hazard ratios (HRs) with 95 % CI for each particle type/agent. In the regression model the time unit was calendar year, and all possible co-variates (the occurrence of COPD, age, and smoking status) were updated annually. The subjects were considered to be under risk from 1990 until whichever came first of the year 2014 (the end of the study), COPD, or death.

For the dose-response relationship analyses, we dichotomized the exposure levels for the different agents into "low" and "high". For each gender, respectively, the geometric mean for each particle was the basis for the cut-off level. Those unexposed to a particle were used as reference group in the HR calculations of COPD after exposure to that specific particle. To calculate dose-response trends we used estimated individual air concentration together with Wald p-values. The unexposed were included in the trend test.

The population attributable fraction (PAF) for COPD from occupational exposure to any of the particles included in the study, as well as from smoking, was estimated by a model-based method so that we could consider the tobacco smoking effect in the same way as in the proportional hazards model. The calculations were conducted for men and women separately, for all cases, for those up an age of 65 years (retirement age in Sweden), and all ages.

4.2 CVD FIELD STUDY

The field study consisted in two parts. In the first part we investigated if occupational particle exposure is affecting common biomarkers for CVD, and in the second part our aim was to study short-term effects on pulse rate and blood pressure when exposed to rapid varying particle levels, but also intermittent noise.

4.2.1 Study design

4.2.1.1 Occupational particle exposure and common CVD biomarkers

The study had a longitudinal design in which we measured exposure levels of particles once at the respective participants' worksite, but biomarkers twice for each participant, at work and directly after summer vacation. In this way we could analyze recovery effects during vacation. However, there were also cross-sectional analyses from the first measurement occasion at work in which we could investigate differences between groups higher and lower exposed to different types of dust.

4.2.1.2 Occupational particle and noise exposure and short-term effects on pulse rate and blood pressure

The study had a longitudinal design during one working day in which we only used data from the first measurements at work. The exposure data used was the particle concentrations of PM 0.1-10 logged every minute and noise levels logged every second. By looking at each of these times we could investigate if there were any acute effects on the outcomes pulse rate and blood pressure.

4.2.2 Study participants

For both studies, to be able to study participants who have occupations where dust as well as noise exposure is present and in different levels, active construction workers were chosen. Within Stockholm County there are also a number of construction sites, both renovating and new building, and we therefore believed it was possible to recruit participants from construction industry within reasonable distance. By collaborating with large construction companies, the Association for Concrete/Stone drillers, Demolition and Decontamination

Workers (Branschföreningen för byggnadsberedning), and the Construction Trade Union (Svenska byggnadsarbetareförbundet) we identified participants with different dust exposure levels and different work tasks. We also conducted two pilot measurements, one on carpenters and one on demolition and decontamination workers.

4.2.2.1 Occupational particle exposure and common CVD biomarkers

The construction workers were classified in occupations high or low exposed to respirable dust. The group high exposed included demolition workers, concrete/stone drillers, concrete workers, bricklayers, and plasterers, and the group low exposed included construction carpenters and plumbers. As smoking is an established risk factor for CVD, only participants who were smoke-free 6 months prior to first measurement at work were included. As there may be sex differences in biomarkers only men were included. Furthermore, inclusion was restricted to construction workers who had worked within the sector for at least 6 months. In this way we were able to investigate dose-response relationships of chronic effects.

4.2.2.2 Occupational particle and noise exposure and short-term effects on pulse rate and blood pressure

For this study, the included participants should have simultaneously measured particle- and noise exposures as well as measured pulse rate and blood pressure over the same working day.

4.2.3 Data collection and analyses

4.2.3.1 Exposure levels

Exposure levels of respirable silica, respirable dust, and dust of all types of particles with a size range of 0.1-10 µm (PM 0.1-10) were measured once at each participant's respective worksite during spring 2019. The first two provided levels for the whole working day, and the last logged exposure levels every minute. We also measured the participants' exposure to noise, logging the A-weighed maximum levels (LAmax) and the C-weighed peak levels (LCpeak) every second. To be able to analyze which type of sound that was associated with changes in the outcomes of blood pressure and pulse rate, respectively, the sound was also recorded. The measures were conducted during a whole workday using personal sampling where the participants carried the measurement equipment. The sampling of respirable silica and respirable dust, as well as the noise and sound equipment were paused during lunch, but not the equipment used for measuring PM 0.1-10. The actual dust exposure levels vary with physical workload, i.e., the heavier workload the more frequent and deeper breaths and hence the more exposure. Therefore, we assessed the participants' average physical workload. Also, as wearing respirator masks and hearing protectors affects the exposure levels, the usage of these protective equipment was noted.
The mass of respirable dust and respirable silica was determined using gravimetric and x-ray diffraction analysis. Thereafter, the sampled air volume was considered, and levels in mg/m^3

were obtained. The levels of PM 0.1-10 in mg/m^3, LAmax in dBA, and LCpeak in dBC were obtained directly from the respective equipment used.

4.2.3.2 Biological markers

Biological sampling was conducted twice for each participant; the same day as exposure measurements at the participants' worksite (March - June 2019), and directly after summer vacation before returning to work (July - September 2019) at Clinic of Occupational and Environmental Medicine, Stockholm County. At both sampling occasions, 50 ml peripheral blood was collected. The blood was centrifugated and serum and plasma separated. The latter two were frozen and all samples were then analysed in the same batch, randomised, to obtain concentrations for each participant of CRP, homocysteine, cholesterol, HDL, LDL, triglycerides, SAA, and fibrinogen. The analyses were conducted by the Department of Clinical Chemistry, Lund University Hospital using routine methods. Resting blood pressure and pulse rate levels were measured three times at both sampling occasions, i.e., before the participants started working/in the morning. Pulse rate was also continuously logged every second and blood pressure was measured every 15 minutes the same day as the exposure measurements while the participants were working.

4.2.3.3 Questionnaire

To obtain additional information about the participants, each individual had to fill in two questionnaires, one at the day of work measurements sampling, and one at the day of summer vacation sampling. The first questionnaire covered information about age, former smoking, alcohol consumption, diet, exercise habits, and former and current work including years in profession as well as occupational anamneses. There were questions about occupational exposures: silica dust, noise, whole-body vibration, hand-arm vibration, working in cold temperature, diesel fumes, chemical vapours/gases, welding fumes, and dust other than silica, as well as physically demanding, and mentally demanding work. Other variables evaluated were exposure to respirable silica and noise from hobbies, prior CVD - including myocardial infarction (MI), angina pectoris, hypertension, stroke, thrombosis in arm/leg, other heart disease, and kidney/urinary disease, diabetes, family history of MI, family history of stroke, family history of hypertension, prescribed medicine use, and non-prescribed medicine use. The second questionnaire included questions about vacation activities, health status, prescribed medicine use, and tobacco use.

4.2.4 Statistical analyses

4.2.4.1 Occupational particle exposure and common CVD biomarkers

In this study, we used two-sample t-tests for continuous and Fischer's exact tests for categorical variables to evaluate differences in characteristics between high and low dust exposed groups. Linear regression analyses with adjustments for age and BMI were performed to evaluate the associations between continuous as well as dichotomized (50th and

75th percentile using the low group as reference) variables of the exposures (respirable silica, respirable dust, and dust of PM 0.1-10), and the outcomes (biomarkers, blood pressure, and resting pulse rate). The effect estimates (β) with 95 % CI represent the modification of each outcome variable with 1 mg/m^3 increase of exposure.
To evaluate the change in outcomes between measurements before and after vacation, with respect to the 75th percentile dichotomized groups, we used paired t-tests. To minimize the probability that our results reflect associations between dust exposure and any other infectious disease or capture those who had altered concentrations of the biomarkers due to CVD-medication, we performed sensitivity analyses only on subjects who on both occasions were not having any infection or using any CVD-related drug. As we were interested in the results of those who actually had not worked prior to the second sampling occasion, we performed sensitivity analyses only on those participants.
To evaluate chronic effects after several working years of occupational exposure to dust above background level, we performed linear regression analyses on working years adjusted for BMI, and age. The effect estimates (β) with 95 % CI then represent the difference of each variable with 1 more working year increase.

4.2.4.2 Occupational particle and noise exposure and short-term effects on pulse rate and blood pressure

In this study, linear regression analyses were performed to analyze the association between the exposures of particles and noise, respectively, and acute changes of pulse rate and blood pressure, respectively. We first conducted a linear regression for each individual, and then we pooled the data and got an overall effect estimate (β). In these analyses, the particles and noise, respectively, and pulse rate were all measured the same time. When analyzing the effect on blood pressure, we used the highest measured levels of particles and noise, respectively, 1-2 minutes prior outcome. The effect estimates (β) with 95 % CI represent the change in pulse rate and blood pressure, respectively, in each particle or noise category. For particles, the categories are quartiles based on all measurements. For LAmax and LCpeak, the categories are 5 dB-intervals.
To investigate if there were different effects on pulse rate if simultaneously exposed to particles and noise, interaction analysis was performed. The exposures were categorized in tertiles with cut-offs for PM 0.1-10 based on all measurements, and for noise in three categories based on previous knowledge: LAmax <75, 75-85, ≥ 85 dBA, and LCpeak <80, 80-90, ≥ 90 dBC.
As we were also interested in knowing if the exposures were present at the same time, we analyzed the correlation between particle and noise exposure with Spearman test.
To be able to analyze if any specific type of sound was associated with pulse rate, we categorized the recorded sound in four categories (impulse sound, sound from machine, sound from object moving, other sound), and performed stratified analyses using linear regression.

4.3 CVD EPIDEMIOLOGICAL STUDY

In the epidemiological part of the AFA CVD-project included in this thesis we wanted to study the association between occupational exposure to different airborne particles/chemicals and first MI in men and women, adjusting for other occupational exposures, individual risk factors, and socio-economy.

4.3.1 Study design

The study was a prospective study with a population-based longitudinal study design.

4.3.2 Study participants

In the study we included individuals with, at minimum, one occupational code between 1985 and 2013, and follow-up of first incident MI up until 2017.

4.3.3 Register-based information / Data collection

The study is based on the Swedish National Cohort on Work and Health (SNOW). It includes all persons who were born between 1930 and 1990 and were working in Sweden at any time between 1985-2013. The cohort was open, and all individuals immigrating were constantly added, and individuals emigrating or dying were constantly removed. In total, 6,437,660 (3,277,421 men and 3,160,239 women) individuals were included in SNOW for all years. In the cohort, various Swedish national registers with high quality were merged. The foundation was Statistic Sweden's Register of the whole total population (RTB) from which data of vital status, emigration, and immigration was retrieved. By matching on personal identification number other information from other Statistic Sweden's registries were added. Occupational history was retrieved from the Occupational register within the LISA (see section 4.1.3) and the National censuses. In this study we used data from the 1980, 1985, and 1990 censuses. Socioeconomic data (income, education) was also retrieved from LISA. Variables varying over time (age, educational level, civil status) were continuously registered in the cohort. Data on individual risk factors for MI, namely smoking and BMI, was retrieved from three subsets of the cohort, namely the Medical Birth Register (MFR) at the National Board of Health and Welfare, the Conscription Register at the Swedish Defense, Conscription and Assessment Agency, and the cohort WOLF (Work, Lipids and Fibrinogen). MFR is a register of women who give birth, and in this study, we used data from the years of 1982-2017. The Conscription register is a register of (mostly) men who compulsory enroll for military service, and in this study, we used data of year 1969. WOLF is a cohort of both men and women born 1922-1983 who were employed in various companies in the three Swedish regions Stockholm, Västernorrland and Jämtland, and information regarding the included participants was collected in 1992-1995 in Stockholm, and in 1996-1998 in Västernorrland

and Jämtland.
From the National board of health and welfare's registers the National Patient Register and the National Cause of Death Register, those individuals diagnosed with MI according to the International Classification of Diseases (ICD) versions 7-10 (ICD10: I21; ICD9: 410; ICD8: 410; ICD7: 420,1 and 420,17) for the period 1986 to 2017 was collected and classified as cases.

4.3.4 Exposure assessment and job exposure matrices

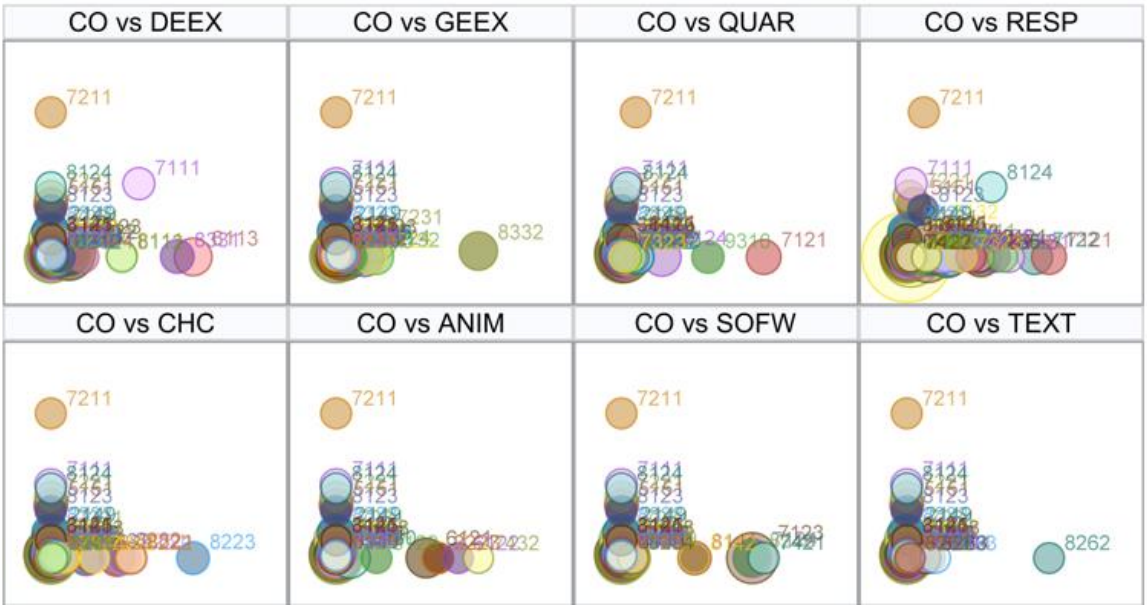
The occupation the respective study participant had each specific year included in this study (1985-2013) was coded according to the Swedish occupational coding system NYK for the years 1985-1996, and according to SSYK96 for the years 1997-2013 using a 4-digit code. To assess particle/chemical exposure we linked the individuals' occupational codes to the Swedish Job Exposure Matrix (SWEJEM). SWEJEM is based on the Finnish FINJEM, with later adaptions to Swedish conditions, and includes data on the intensity and probability for the years 1945-2014 for each exposure in each occupation. The data is based on exposure measurements in Sweden and other countries in the Nordic and expressed as averages of 8h workdays in mg/m^3, $\mu g/m^3$, $fibres/cm^3$, ppm, or µmol in blood. There were 41 particles and chemicals/groups of interest in this study, divided in nine categories:
- combustion compounds (diesel engine exhaust, gasoline engine exhaust, PAH including BAP, bitumen fumes, SO2),
- gases (CO, volatile sulfur compounds),
- metals (arsenic (As), cadmium (Cd), chromium (Cr), iron (Fe), lead (Pb), nickel (Ni)),
- irritants (formaldehyde, oil mist),
- solvents (aliphatic/alicyclic hydrocarbon solvents (ALHC), aromatic hydrocarbon solvents (ARHC) including benzene, toluene, and styrene; chlorinated hydrocarbon solvents (CHC) including methylene chloride (MCH), perchloroethylene (PER), trichloroethylene (TRI); gasoline),
- welding fumes,
- inorganic dust and fibres (quartz dust, asbestos, man-made mineral fibres),
- organic dust (dust from animal, flour, leather, plant, pulp or paper, synthetic polymer, textile, and wood including softwood and hardwood), and
- respirable dust.

To be able to adjust for other occupational exposures we linked the individuals' occupational codes to three other JEMs, namely a JEM for psychosocial workload, a JEM for physical workload, and a noise-JEM. The former two are based on surveys conducted biennially 1989-2013 by Statistic Sweden. In the study we adjusted for psychosocial workload by using an index of decision authority, and for physical workload by using an index of physical load on the musculoskeletal system. To be able to adjust for occupational exposure to noise, we used a noise-JEM. In this latter JEM the occupational annual 8h average exposure levels are expressed in dBA for 321 occupations and presented in five-year intervals. In this study we

attached data for the years 1985-2013. Mostly, a 4-digit SSYK96-code was used for linking these JEMs.

For some particles/chemicals in recent-exposure analyses, we adjusted for confounder particles/chemicals. We based our decision on which particles/chemicals in the recent-exposure analyses to further adjust for if they a) had a dose-response effect in the analyses adjusted by decision authority index, physical workload index, and noise, and b) if they have established risk factors from literature. The confounder particles/chemicals were chosen if they correlate but not too much with the exposure particle/chemical of interest. These correlations were investigated with bubble scatter graphs, see an example in Figure 3.

Figure 3*. Example of bubble scatter graphs in a matrix for CO*



4.3.5 Statistical analyses

As in study I we used a discrete time proportional hazard model to analyze the associations between the different particles/chemicals and first MI. The risks for each particle/chemical were calculated as HRs with 95 % CI for the whole population and separate for men and women, both for exposure one year prior first MI (recent exposure) and for cumulative exposure for several years. We calculated the crude HRs and then HRs additionally adjusted for the other occupational exposures of decision authority index, physical workload index, noise, and in the analyses of exposure one year prior MI confounding particles/chemicals. The time unit was calendar year, and all variables were updated annually. To enter the cohort, the subject had to have an occupational code and for each year an income which was higher than half of the sex-specific median or 1/3 of the median income for both sexes for that occupation.

In our analyses we defined occupations as exposed if the prevalence was ≥ 50% and included all intensity levels. For exposure we used the product of prevalence and intensity of the respective particle/chemical.
In the exposure one year prior MI-analyses, we conducted calculations of dose-response relationships. This was done by dichotomizing the intensity levels for each particle/chemical as "below" or "above" the median level, either for both sexes, or for men and women separately. Those unexposed and with a prevalence of < 50% were used as reference group. The other occupational exposures of lack of decision authority, physical workload, and noise used a full-scale with 5 categoric level-groups with 4 dummies when adjusting.
In the cumulative exposure-analyses, the sum of exposure of particles/chemicals in all calendar years before the MI were used to calculate the effect. This sum of exposure was compared to the sum of exposure of not having MI that year. The other occupational exposures used for adjusting were divided in quintiles. Those subjects in the two highest/worst quintiles were defined as exposed to lack of decision authority and physical workload, as well as those exposed to > 80 dBA of noise. The sum of number of years in these quintiles were then used in the analyses for each subject.

To investigate if individual risk factors of smoking and BMI affected the results, we additionally adjusted for these covariates in the recent-exposure analyses in the subsets of Medical Birth Register, Conscription Register, and WOLF.

Stratified analyses for those with the highest attained educational level being up to 3-year secondary school was also performed for five particles/chemicals which in the cumulative exposure-analyses had increased risks of MI.

The attributable fraction (AF) of all (both sexes) recently (one year prior MI) exposed to the particles/chemicals were calculated. This was done by re-running the analyses and changing exposed to unexposed for the particle/chemical of interest. The difference of number of cases divided by the number of exposed cases is the AF.

4.4 ETHICAL CONSIDERATIONS

4.4.1 COPD study and CVD epidemiological study

In both study I and IV data were collected prior to and independent of the studies. It is impossible to ask for consent from persons enrolled in the registers for the respective study. To protect the integrity of the study participants, the analyses, storing and using of data have therefore been carefully considered. Information about participants was already coded and no personal identification number or name was used and known to me or anyone else in the research groups. The data was only accessible for the research teams and stored at servers based at Karolinska Institutet. Furthermore, the results from the studies have been reported so

that the identity of any participant could not be revealed. Results have therefore been presented on group-level, for example for specific particles and chemicals. The GDPR (General Data Protection Regulation, EU 2016/679) requirements regarding personal data have been followed in both studies, and the work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The regional ethics committee in Stockholm, Sweden, approved both projects (COPD-study: (Diary No. 2016/500-31/1, and CVD epidemiological study: Ref. No. 2018/1298-31/2).

Throughout research one should also follow some general rules. Telling the truth about the research and openly account for methods and results are crucial. Within the studies, we accurately state what and how we have done in the section "material and methods" as well as the outcome in the "results-section" in the respective manuscript. In the manuscripts' "discussion"-sections, pros and cons with the methods used and the results are also highlighted.

4.4.2 CVD field study

One could argue why animal studies are not preferable instead of a field study on humans, since earlier animal testing have showed that silica dust has toxic effects, and earlier studies have also shown adverse effects in humans. However, as we wanted to investigate effects in real working life situations with today's exposure levels of different dusts as well of intermittent noise this was not appropriate as it is very hard to imitate. Therefore, this study was conducted on humans. The study was performed in line with the principles of the Declaration of Helsinki, and approval was granted by the Regional Ethics Committee, Stockholm, Sweden (Ref. No. 2019-00208). The handling of data was regulated by the General Data Protection Regulation (GDPR) (EU 2016/679), and the data also protected by the "Publicity and confidentiality act" (Offentlighets- och sekretesslagen in Swedish, SFS 2009:400) meaning that no unauthorized will be given access to the data. All participants within this study voluntarily agreed and provided written informed consent before their participation. Information was given to the participants, both written and orally, along with a consent form, about the background of study, its rationales and purposes, the samples needed, the handling of biological samples and confidential personal data, and insurance of the participants' privacy. Furthermore, potential risks of discomfort due to sampling was stated. Information was given that the results from the study would be presented at group level, hence no individual findings. The right to withdraw from the study at any time without any explanation was clearly stated, and that we then would remove and destroy or unidentify all gathered information and samples regarding the participant. Furthermore, the participant could approve or disapprove if their samples could be stored for other, future research projects.

Feedback to participants and their employers is also of importance, and essential for trust to the research as a whole and the specific study. Therefore, the participants received a letter

with their results of blood pressure and cholesterol level. If some biological results which may be of interest to the participant was deviating from normal values (for example cholesterol) the responsible physician also contacted some of the participants regarding these findings and/or information was stated in the letter that the participant was advised to contact their general practitioner or health care clinic. Furthermore, we also reported each company's exposure levels in written reports and communicated via smaller meetings with the companies.

In this study, the number of participants, who could suffer from discomfort and worries, was relatively small (n=65). Though, the number of persons who would benefit from the objectives of the study are much larger, with for example approximately 85,000 persons exposed to respirable silica in Sweden (more than 3 million in Europe) (54). The objectives being to gain knowledge if today´s Swedish OELs regarding respirable crystalline silica dust, respirable inorganic dust, as well as noise levels of LAmax and LCpeak are protective and thereby improve risk assessments in working life.

5 RESULTS

The same results from the respective studies on occupational particle exposure and COPD or CVD, respectively, are presented here, but partly in a new approach, as well as focusing on particle exposure and not noise in study III. For more details, please see the corresponding papers.

5.1 COPD STUDY

The study included 43,641 subjects of which 2,131 or 4.9 % (1,201 women and 930 men) was considered as COPD cases according to our criteria. The mean age of being diagnosed with COPD was among men 65.2 (standard deviation 9.1) years and among women 64.5 (standard deviation 9.4) years.

5.1.1 Characteristics of the study population

In 1990, most exposed subjects, both men and women, were 40-59 years of age. As expected, more persons (higher proportions) with COPD were smokers in both sexes (men: 86 % of those exposed and 88 % of those unexposed to the study's included particles, women: 82 % both of those exposed and unexposed to the study's included particles) compared to persons not having COPD and not smoking (men: 43 % of those exposed and 49 % of those unexposed to the study's included particles, women: 52 % of those exposed and 50 % of those unexposed to the study's included particles). Also, compared to persons with COPD who were not exposed, both male and female exposed cases who smoked had done so for some more pack-years (men: 26 vs 23, and women: 21 vs 20).

The educational level in 1990 was similar in both genders with 63 % attained pre-secondary or secondary school (i.e., low) as the highest attained level. The group which was occupationally exposed to particles and being COPD cases had the greatest proportion of persons with low-level education in both genders (men 90 %, women 93 %). For more details, see study I in the back of this thesis.

5.1.2 Occupational particle exposure and COPD

The number and proportion of exposed participants, as well as the proportion of participants exposed to two particle types was investigated for each sex. For example, some men exposed to diesel engine exhaust (2,444 subjects) were also exposed to oil mist (20 %) and to welding fumes (13 %). Nearly half of all men and one third of women respectively exposed to welding fumes were also exposed to oil mist (men 45 %, women 31 %), and almost all were also exposed to iron dust (men: 99 %, women: 100 %).

Supplementary table 1 presents HR with 95 % CI including dose-response relationships for COPD in men and women based on exposure, to groups of agents, and to all the included agents separately. The results show a significantly smoking-adjusted increased risk of COPD among men occupationally exposed to any type of inorganic (HR 1.39, CI 1.15–1.67) or any organic (HR 1.33, CI 1.12–1.56) particles, as well as high exposure levels to any combustion particles (HR 1.25, CI 1.00–1.56), and welding fumes (HR 1.57, CI 1.12–2.21). Among women exposure to any type of organic particles (HR 1.22, CI 1.01–1.47) was significantly associated with a smoking-adjusted risk of incidence of COPD, especially in the high-exposed group (HR 1.28, CI 1.01–1.64).
Among the specific agents there was a significant association in men highly exposed to RCS (HR 1.63, CI 1.17–2.27) and other inorganic dusts and fibres (HR 1.56, CI 1.15–2.13) with positive dose-response relationships. Also, men highly exposed to asphalt/bitumen particles (HR 1.71, CI 1.06–2.76), and welding fumes (HR 1.57, CI 1.12–2.21) had elevated risks of COPD with dose-response relationship tendencies. There was an elevated risk of COPD in both genders after exposure to paper dust (men HR 1.39, CI 1.01–1.93, women HR 1.56, CI 1.08–2.25), though the low exposed had higher risk than the high exposed. Men exposed to cooking fumes (HR 2.21, CI 1.14–4.27), and women high exposed to other organic particles (HR 1.53, CI 1.15-2.04) also had increased risks of COPD. Furthermore, men both exposed to all levels (HR 1.18, CI 0.99–1.41) and specifically the highly exposed (HR 1.24, CI 0.98–1.56) to diesel exhaust, had a borderline significant risk of COPD, and there was a significant positive dose-response trend.

Supplementary table 1 also presents the calculated mean exposure concentration for a working day of 8 hours for each particle/agent. For example, for men an exposure to the average level 0.052 mg/m^3 of RCS or 0.805 mg/m^3 of welding fumes are significantly associated with an elevated risk of COPD after adjusting for smoking.

We used the JEM to identify occupations with particle exposures which were associated with an elevated risk of COPD. Within some occupations the workers are exposed to several particles/agents and therefore these occupations re-occurred several times. Table 1 presents occupations with 5 or more cases of COPD, for men and women separately, based on grouping of particles in inorganic/organic and combustion/welding. Among men, occupations within construction industry such as welders and flamecutters and floor layers had these particle exposures, but also other occupations. Among women, those who worked in the service sector with occupations such as cleaners and cooks, but also store and warehouse workers were exposed to particles associated with increased risks of COPD incidence. In some occupations, the proportion of workers having COPD are high, for example female store and warehouse workers (15 %).

Table 1. Occupations with 5 or more cases of COPD, for men and women separately

Men			**Women**		
Occupation	**P** [a] **(%)**	***n*** **COPD**	**Occupation**	**P** [a] **(%)**	***n*** **COPD**
Inorganic/Organic particles			*Inorganic/Organic particles*		
Welders and flamecutters	12.5	6	Store and warehouse workers	15	16
Horticultural workers	12.2	9	Cleaners	9.4	51
Floor layers	11.9	5	Cooks	6.4	11
Combustion/Welding			*Combustion/Welding*		
Road transport supervisors	12.8	5	Waiters	7.6	12
Welders and flame cutters	12.5	6	Kitchen assistants, restaurant workers	5.5	23
Truck and conveyor operators	11.7	7			

[a] Proportion of workers within the occupation with COPD

5.1.2.1 Population Attributable Fraction

The population attributable fractions (PAFs) from occupational exposure to all particles included in this study and smoking, respectively, are presented in Table 2. The PAF from particles was approximately 6 % for all subjects, both in all ages and for those with cases younger than 65 years (age of retirement). For the younger group (< 65 years) the PAF from particles was 2.78 % for women and more than three times that much for men, 10.61 %. The same was seen for all ages with PAF for women being 2.79 % and for men being 9.94 %.

Table 2. Population attributable fraction for COPD from occupational particle exposure, and smoking, respectively

	All		**Men**		**Women**	
	PAF [a] (%)	95 % CI	PAF [a] (%)	95 % CI	PAF [a] (%)	95 % CI
All cases						
Particles [b]	5.92	3.68-8.28	9.94	5.61-14.70	2.79	0.59-5.04
Smoking	68.02	65.03-71.36	69.45	64.62-74.42	66.90	63.03-70.96
Cases < 65 years						
Particles [b]	6.08	3.71-8.62	10.61	5.65-15.76	2.78	0.48-5.00
Smoking	72.44	69.71-75.50	71.32	66.57-76.10	73.27	69.85-76.86

[a] Population attributable fraction

[b] From inorganic, organic, combustion particles and welding fumes

Table originally published in Grahn K, Gustavsson P, Andersson T, Lindén A, Hemmingsson T, Selander J, Wiebert P (2021) *Occupational exposure to particles and increased risk of developing chronic obstructive pulmonary disease (COPD): A population-based cohort study in Stockholm, Sweden*, Environmental Research, doi.org/10.1016/j.envres.2021.111739 and is licensed under a Creative Commons Attribution (http://creativecommons.org/licenses/by/4.0/)

5.2 CVD FIELD STUDY

Study II is based on 65 non-smoking male construction workers, and study III on 46 of those participants.

5.2.1 Characteristics of the study population

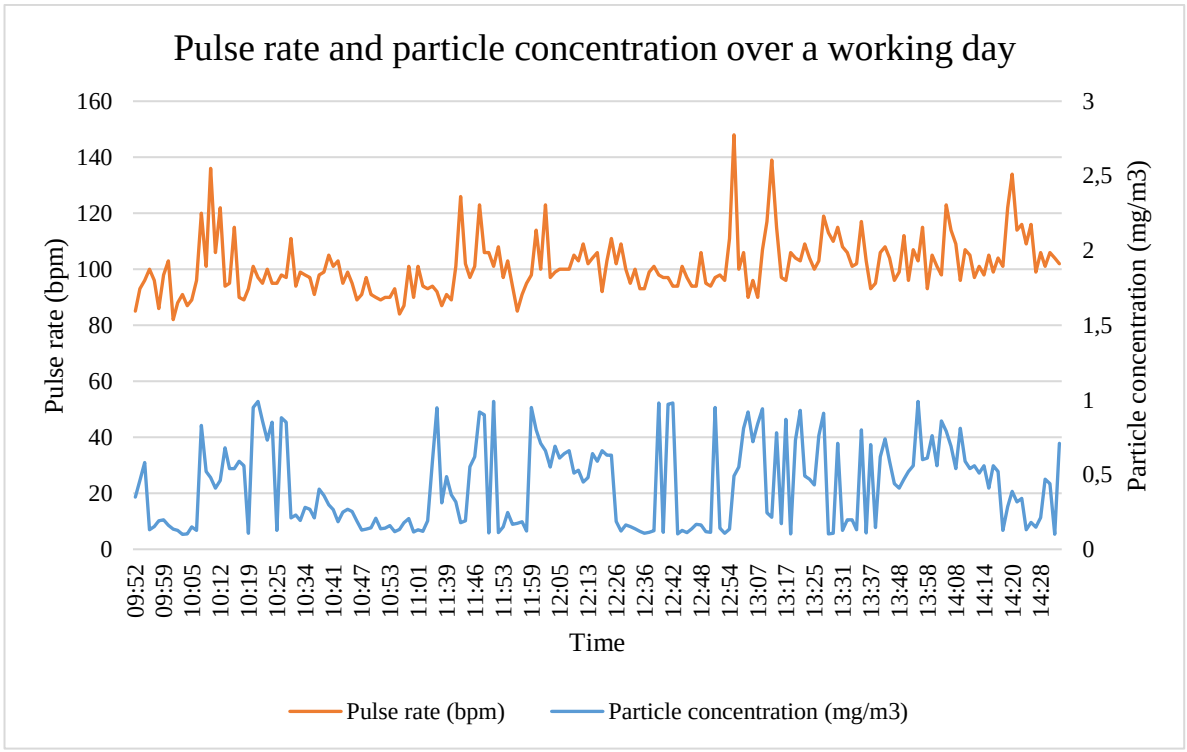
5.2.1.1 Occupational particle exposure and common CVD biomarkers

For this study, study II, the included 65 participants, aged 20-65 years, were stratified in *a priori* categorized occupational groups that were high (n = 36) or low (n = 29) exposed to respirable dust. The two groups did not significantly differ except from whole body vibration exposure and respiratory mask use where the high exposed group had a higher occurrence. We also stratified on the 75th percentile of the three measured dust concentrations to get a contrast in characteristics between high and low exposed workers. Workers high (n=16) and low (n=49) exposed to respirable dust had no significant differences in characteristics, apart from a lower alcohol consumption and higher physical activity in the high-exposed group. Those high (n=16) exposed to respirable silica had done fewer years in dust-exposed jobs and were younger in comparison with their lower exposed colleagues (n=49). For more details, see study II in the back of this thesis.

5.2.1.2 Occupational particle and noise exposure and short-term effects on pulse rate and blood pressure

In this study, study III, out of the 65 participants, 46 were included who all had simultaneously measured exposure levels of dust of PM 0.1-10 and noise, sound recordings as well as logged variations of pulse rate, and blood pressure. These participants were between 20 and 65 years of age, 40 % were ever-smokers with a mean of 9.4 smoking years, and 17.4 % reported using prescribed medicine. A sixth (17 %) used respiratory masks, and almost all (94 %) used hearing protectors during the day of measurements. From questionnaire answers a majority also reported being occupationally exposed to hand-arm vibrations, cold temperature, and having physically demanding and psychosocially demanding work. Logged measurements of PM 0.1-10 and pulse rate show how these vary over the day, see Figure 4.

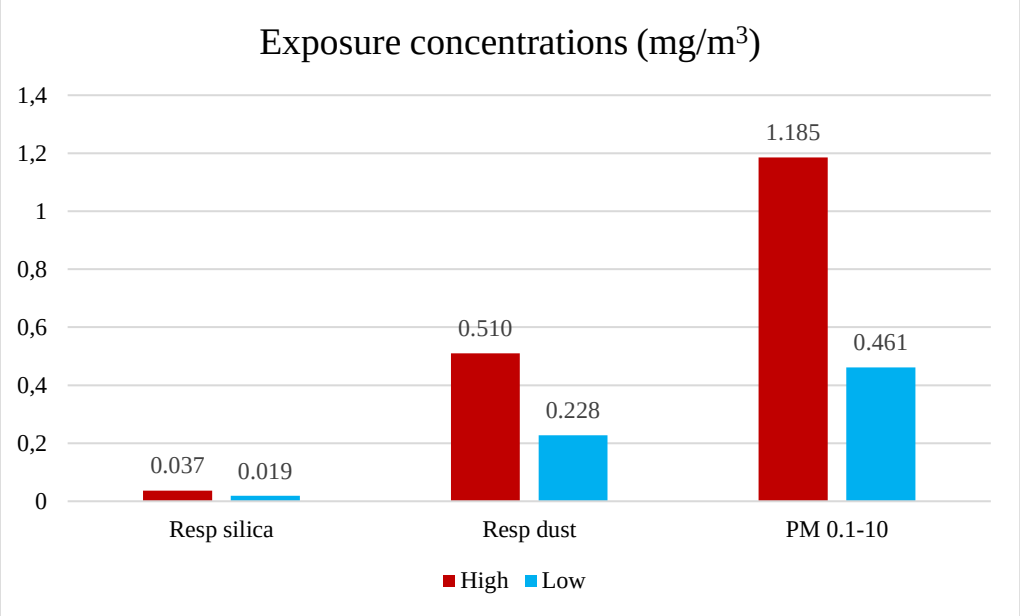
***Figure 4**. Variations of PM 0.1-10 and pulse rate over the working day for one of the study participants*



5.2.2 Occupational particle exposure and common CVD biomarkers

We managed to get a contrast in exposure levels between the two *a priori* decided occupational groups low and high, see Figure 5. For both respirable silica and respirable dust, the mean exposure levels were about twice as high in the high group as in the low group, and for dust of PM 0.1-10 the mean level was two and a half times that in the low group. However, the levels overlapped between the groups and were skewed to the right. A few very high exposed participants influenced the mean levels in the high group. The mean levels in each group did not reach the Swedish OELs for respirable silica (0.1 mg/m^3) or respirable inorganic dust (2.5 mg/m^3) (10). The mean levels of exposure for all participants was for respirable silica 0.027 mg/m^3, for respirable dust 0.354 mg/m^3, and for those participants in which we measured PM 0.1-10 it was 0.788 mg/m^3.

***Figure 5**. Mean exposure levels of respirable silica, respirable dust, and particles of PM 0.1-10 of the a priori decided occupational groups high (demolition workers, concrete/stone drillers, concrete workers, bricklayers, and plasterers) and low (construction carpenters and plumbers).*



In the cross-sectional analyses with data only from the first measurements at work, the concentrations of homocysteine were higher the higher exposure levels of the three particle types. HDL was significantly negatively and resting pulse rate significantly positively associated with respirable dust and PM 0.1-10, see Table 3. Also, in sensitivity analyses when we adjusted for the potential confounders alcohol consumption and physical activity, as well as for viral infections at the time of biological sampling and usage of CVD-related drugs, the results were similar as in the main analyses.

Table 3. Effect estimates expressed as β-values with 95 % confidence intervals (CI). The β represents the change in each variable with an increase in exposure of 1 mg/m^3.

	Respirable silica continuous variables		**Respirable dust continuous variables**		**Dust of PM 0.1-10 continuous variables**	
	Adj β [a]	95 % CI	Adj β [a]	95 % CI	Adj β [a]	95 % CI
Systolic blood pressure (mm Hg)	-11.93	-100.63, 76.77	0.88	-7.37, 9.14	1.78	-1.96, 5.51
Diastolic blood pressure (mm Hg)	-13.01	-84.68, 58.65	0.98	-5.69, 7.65	1.31	-1.37, 3.99
CRP (mg/L)	0.74	-17.81, 19.29	0.68	-1.04, 2.39	0.23	-0.54, 1.01
Homocysteine (µmol/L) [b]	**25.22**	**2.97, 47.48**	**2.24**	**0.16, 4.33**	**1.20**	**0.22, 2.18**
Cholesterol (mmol/L)	-1.96	-7.99, 4.07	-0.27	-0.83, 0.29	-0.11	-0.37, 0.15
HDL (mmol/L)	-1.11	-3.20, 0.99	**-0.22**	**-0.41, -0.03**	**-0.09**	**-0.19, -0.00**
LDL (mmol/L)	-0.82	-6.01, 4.37	-0.18	-0.66, 0.30	-0.05	-0.27, 0.18
Triglycerides (mmol/L)	-1.53	-10.03, 6.96	0.00	-0.79, 0.80	-0.01	-0.43, 0.40
Pulse, resting (bpm)	28.77	-38.70, 96.24	**8.09**	**2.13, 14.06**	**3.77**	**1.07, 6.46**
SAA (mg/L)	-1.38	-21.60, 18.83	-0.10	-1.98, 1.78	0.10	-0.73, 0.92
Fibrinogen (g/L)	1.60	-1.76, 4.97	0.15	-0.17, 0.46	0.07	-0.09, 0.23

[a] Linear regression, adjusted for age and BMI, [b] 1 missing

In the longitudinal analyses on differences between the measurements during work and after vacation there were some significant results. Workers high exposed (≥ 75 % percentile) to all three particle types all had higher systolic blood pressure during work than after vacation, and those high exposed to respirable dust also had higher diastolic blood pressure at the first measurement (mean change systolic 4.87 mmHg, diastolic 3.98 mmHg). Furthermore, all but those high exposed to PM 0.1-10 had higher concentrations of LDL during work than after vacation, largest mean change 1.54 in the group high exposed to respirable dust. At the same time, the concentrations of HDL did not change markedly. See study II in the back of this thesis for more details. Notably, homocysteine concentrations did not differ indicating no recovery effect during vacation. Also here, the results from these main analyses were similar as those in sensitivity analyses of workers not using CVD-related drugs, not having any infection at any sampling occasion, and still being on vacation at the second measurement.

In analyses on number of years in dust-exposed jobs and considering age and BMI by adjusting for these confounders, the concentrations of homocysteine and LDL increased with every year of working, 0.11 µmol/L and 0.03 mmol/L, respectively. For long-term results, see Table 4.

Table 4. Long-term change (β with 95 % CI) in blood pressure, pulse rate and biomarkers associated with years of occupational particle-exposure, adjusted for age and BMI. The β represents the difference in each variable with one more working year increase.

	Crude β	95 % CI	Adj β (BMI [a], age)	95 % CI
Systolic blood pressure (mm Hg)	0.16	-0.13 - 0.45	-0.03	-0.40 - 0.34
Diastolic blood pressure (mm Hg)	0.19	-0.05 - 0.43	-0.12	-0.42 - 0.17
CRP (mg/L)	0.00	-0.06 - 0.06	-0.03	-0.10 - 0.05
Homocysteine (µmol/L)	0.06	-0.01 - 0.13	**0.11**	**0.02 - 0.21**
Cholesterol (mmol/L)	0.03	0.01 - 0.05	0.01	-0.01 - 0.04
HDL (mmol/L)	0.00	-0.00 - 0.01	0.00	-0.01 - 0.01
LDL (mmol/L)	0.03	0.01 - 0.04	**0.03**	**0.01 - 0.05**
Triglycerides (mmol/L)	-0.00	-0.03 - 0.03	-0.03	-0.06 - 0.01
Pulse rate, resting (bpm)	0.06	-0.15 - 0.28	-0.08	-0.36 - 0.20
SAA (mg/L)	0.05	-0.01 - 0.12	0.03	-0.05 - 0.11
Fibrinogen (g/L)	0.01	-0.00 - 0.02	-0.00	-0.02 - 0.01

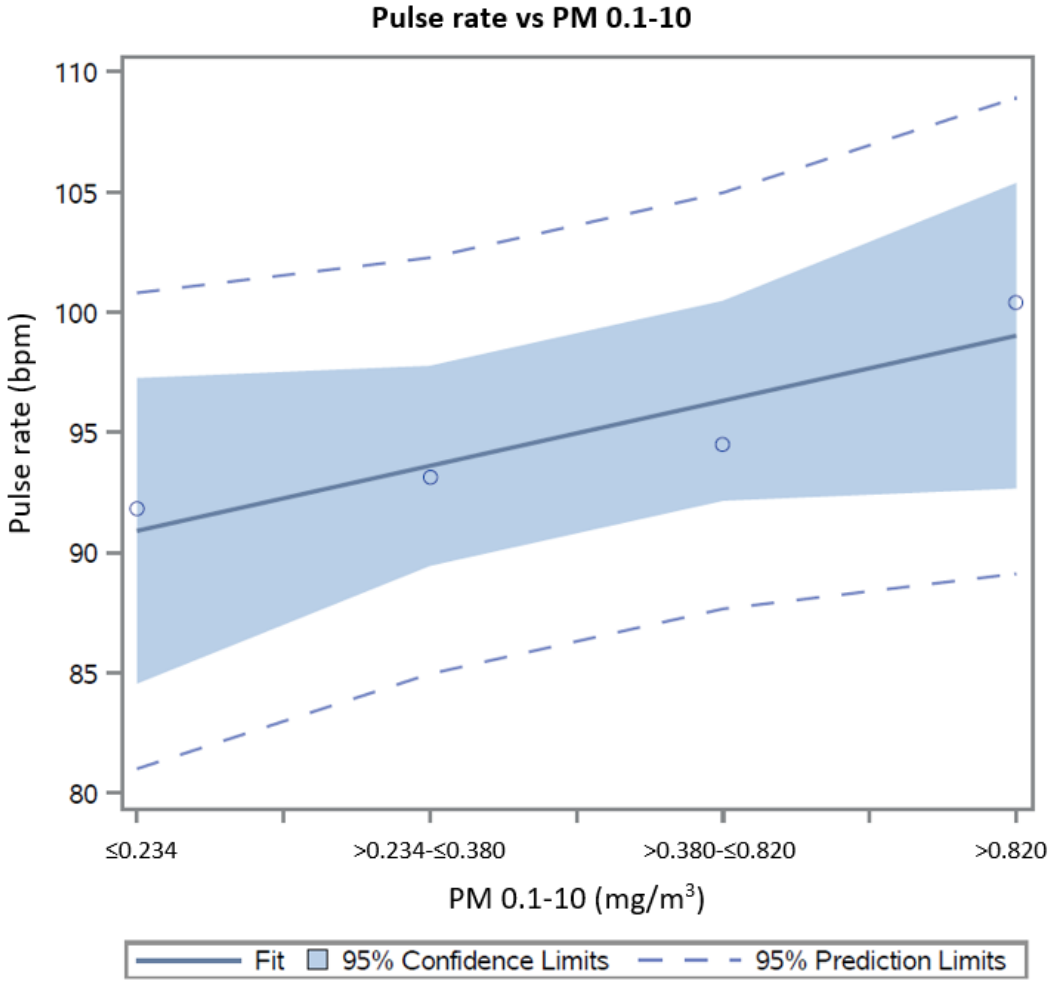
[a] Body mass index

Table adapted from supplementary material to Grahn K, Broberg K, Gustavsson P, Ljungman P, Lindfors P, Sjöström M, Wiebert P, Selander J (2022) *Occupational exposure to particles and biomarkers of cardiovascular disease – during work and after vacation*, International Archives of Occupational and Environmental Health, doi.org/10.1007/s00420-022-01900-5 and is licensed under a Creative Commons Attribution (http://creativecommons.org/licenses/by/4.0/)

5.2.3 Occupational particle and noise exposure and short-term effects on pulse rate and blood pressure

Our results show a significant association between exposure of PM 0.1-10 above the measured median (0.480 mg/m^3) and acute elevated pulse rate, see Figure 6. The rate being 2.68 bpm higher if exposed to particle concentrations above 0.480 mg/m^3 but less than 0.820 mg/m^3, and 8.57 bpm higher if exposed to particle levels above 0.820 mg/m^3 compared to dust levels below 0.234 mg/m^3. The average increase of pulse rate being 0.40 bpm per 1 mg/m^3 higher particle concentration exposure. Also, noise had a significant association with pulse rate, with the rate increasing with increasing noise levels. At levels > 100 dBA the pulse rate was 7.60 bpm higher compared to exposure levels below 75 dBA.

Figure 6*. Spline on pulse rate vs exposure to dust of PM 0.1-10 for all participants, corresponding to quartiles of dust increments. Circles represent observation within each quartile and the filled linear line adapted to these. Darker area represents 95 % CI, and dashed line the 95 % predicted interval for individual measurements.*



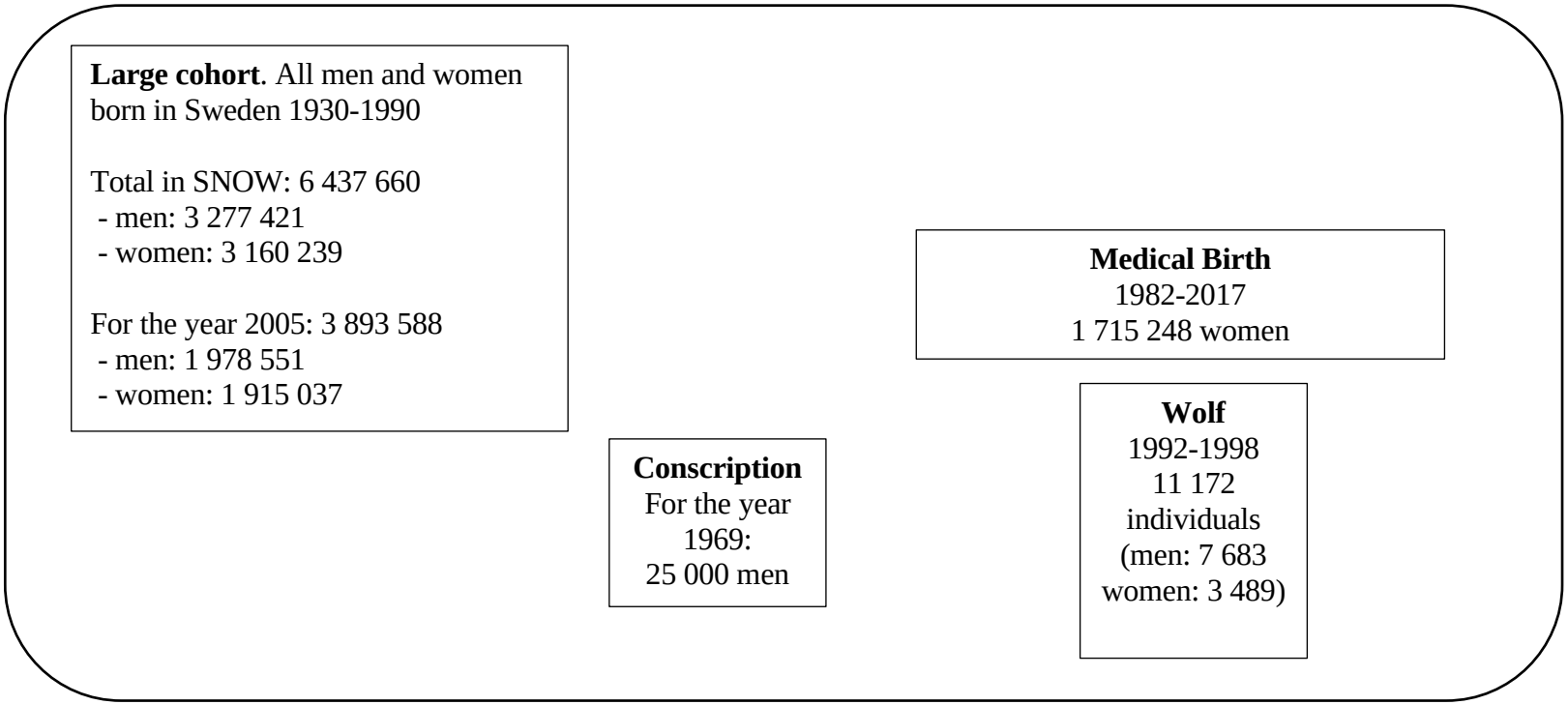
When investigating simultaneous exposure to PM 0.1-10 and noise, the results show an additive effect on pulse rate. For example, compared to reference levels in our analyses of particles and noise (particles ≤ 0.300 mg/m^3 and LAmax < 75 dBA), being exposed to PM 0.1-10 > 0.694 mg/m^3 the pulse rate being 6.59 bpm higher. When also the LAmax level being higher (>= 85 dBA) pulse rate is 13.35 bpm higher compared to reference levels. However, when analysing if the two exposures do occur at the same time, the correlation coefficient is low (0.190 between PM 0.1-10 and LAmax).

Our results did not show any significant associations between either PM 0.1-10 or noise exposure and blood pressure. Nor was there any specific type of sound associated with change in pulse rate.

5.3 CVD EPIDEMIOLOGICAL STUDY

The CVD epidemiological study on particle/chemical exposure and first MI was based on the SNOW cohort which includes millions of subjects. Data from several cohort were added. Figure 7 presents number of included participants and the sources.

Figure 7*. Included cohorts and registers in study IV and example of number of included participants*



5.3.1 Characteristics of the study population

The characteristics is presented for the example year of 2005 because it is reflecting the particle/chemical exposure levels in most of the follow up period. This year, nearly 3.9 million subjects, 2 million men and 1.9 million women, were included and were having an occupation. Overall, men were more exposed to particles/chemicals than women. For some particle/chemical groups, exposure to lack of decision authority, physical workload, and noise were high. For example, among men and women exposed to inorganic particles 42.6 % and 38.2 %, respectively, were exposed to high levels of lack of decision authority. More than two thirds of both men and women exposed to all types of particle/chemical groups were heavily exposed to physical workload. Also, a large portion of both men and women, except those exposed to combustion compounds, gases, and solvents, and women exposed to organic and respirable dust, were heavily exposed to noise above 80 dBA, see Table 5.

Table 5. Characteristics for subjects of all ages exposed to particles/chemical groups for the year 2005. Numbers and *proportion (%)* of exposed to the respective groups, when the respective included particle/chemical in the group had a prevalence ≥ 50 %. All intensity levels included.

	Combust comp [a]	**Gases**[b]	**Metals**[c]	**Irritants**[d]	**Solvents**[e]	**Welding fumes**	**Inorg dust** [f]	**Org dust** [g]	**Resp dust** [h]
Sex									
men	187046	87490	116236	47259	30294	39105	97199	164567	350802
	(9.5)	*(4.4)*	*(5.9)*	*(2.4)*	*(1.5)*	*(2.0)*	*(4.9)*	*(8.3)*	*(17.7)*
women	32556	8590	8154	7913	14751	623	2534	39226	65429
	(1.7)	*(0.4)*	*(0.4)*	*(0.4)*	*(0.8)*	*(0.0)*	*(0.1)*	*(2.0)*	*(3.4)*
Decision[i]									
men	21410	20459	1911	215	16396	0	41433	68028	101622
	(11.4)	*(23.4)*	*(1.6)*	*(0.5)*	*(54.1)*	*(0.0)*	*(42.6)*	*(41.3)*	*(29.0)*
women	4553	5159	179	54	14629	117	969	14898	23791
	(14.0)	*(60.1)*	*(2.2)*	*(0.7)*	*(99.2)*	*(18.8)*	*(38.2)*	*(38.0)*	*(36.4)*
Physical[j]									
men	127636	69503	100634	44818	25259	36853	85404	145485	272021
	(68.2)	*(79.4)*	*(86.6)*	*(94.8)*	*(83.4)*	*(94.2)*	*(87.9)*	*(88.4)*	*(77.5)*
women	31443	7867	7592	6651	9999	556	1819	31944	61128
	(96.6)	*(91.6)*	*(93.1)*	*(84.1)*	*(67.8)*	*(89.2)*	*(71.8)*	*(81.4)*	*(93.4)*
Noise[k]									
men	19081	37885	113731	47044	3560	39105	87315	110107	245785
	(10.2)	*(43.3)*	*(97.8)*	*(99.5)*	*(11.8)*	*(100.0)*	*(89.8)*	*(67.3)*	*(70.1)*
women	2335	2419	8123	6902	410	623	2415	11064	21142
	(7.2)	*(28.2)*	*(99.6)*	*(87.2)*	*(2.8)*	*(100.0)*	*(95.3)*	*(28.2)*	*(32.3)*

[a] Combustion compounds: diesel engine exhaust, gasoline engine exhaust, PAH, BAP, bitumen fumes, SO2

[b] Gases: CO, volatile sulfur compounds

[c] Metals: As, Cd, Cr, Fe, Pb, Ni

[d] Irritants: formaldehyde, oil mist

[e] Solvents: aliphatic/alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents (including benzene, toluene, styrene), chlorinated hydrocarbon solvents (including methylene chloride, perchloroethylene, trichloroethylene), gasoline

[f] Inorganic dust: quartz dust, asbestos, man-made mineral fibers

[g] Organic dust: animal dusts, flour dust, leather dust, plant dust, pulp or paper dust, synthetic polymer dust, textile dust, wood dust (including softwood dust, hardwood dust)

[h] Respirable dust

[i] Decision authority index, two highest quintiles

[j] Physical workload index, two highest quintiles

[k] Noise ≥ 80 dBA

5.3.2 Occupational particle and chemical exposure and MI

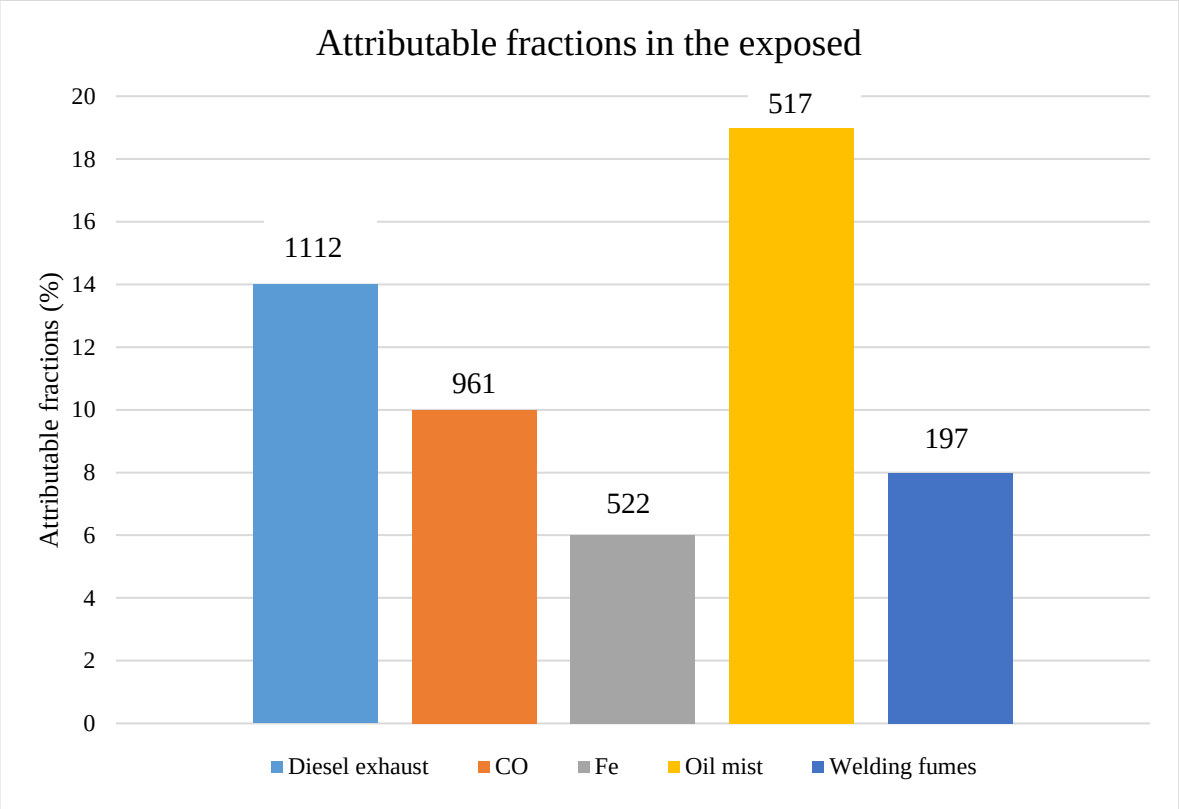
This study included a total of 103,436 incident cases of first MI. There were increased risks of first MI when exposed to several particles/chemicals, both after recent (one year prior MI) exposure and cumulative exposure for several years, even after adjusting for other occupational exposures of lack of decision authority, physical workload, noise, and for some particles/chemicals confounding chemicals. For more details, see study IV in the back of this thesis. Adjusting for smoking and BMI, which are life-style risk factors, changed the risk estimates very little in the recent exposure analyses in subsets of the cohort. Also, results from stratified analyses on subjects with low level of education showed risk estimates similar as results from analyses on subjects with all levels of education.

5.3.2.1 Recent exposure

For the whole study population (and mostly for men), after adjusting for other occupational exposures, increased risks of MI were seen for diesel engine exhaust, SO2, Cd (all three with an inverse dose-response relationship), PAH including BAP, CO, volatile sulfur compounds, Fe, formaldehyde, welding fumes, asbestos, and flour dust (all nine with a dose-response relationship). Additionally, women had elevated risks for MI when exposed to lower levels of Pb and higher levels of pulp and paper dust.

In the whole study population, the attributable fractions for first MI were highest for those who were exposed to oil mist, diesel engine exhaust, CO, welding fumes, and Fe. In Figure 8 the attributable fractions are presented, and also the number of cases which would have been prevented if there was no exposure to the respective agent.

Figure 8. *Attributable fractions for first MI in the exposed to particles/chemicals in the whole study population of both sexes. Number of cases prevented if there was no exposure to the respective agent is included.*



5.3.2.2 Cumulative exposure

For both men and women, after adjusting for other occupational exposures of lack of decision authority, physical workload, and noise, elevated risks of first MI in all ages (20+ years) were found for cumulative exposure of gasoline engine exhaust, PAH including BAP, and SO2, all *combustion compounds*. Both sexes also had significantly higher risks of first MI in all ages if exposed to the *gases* CO and volatile sulfur compounds, to the *metals* Cd, Cr and Pb, to the *irritant* oil mist, and to respirable dust. Our results also indicated significantly higher risks for men exposed to diesel engine exhaust, benzene, gasoline, flour dust, and pulp and paper dust, and for women exposed to Fe, welding fumes, quartz dust, and wood dust. However, among men there were nearly significant increased risks associated with exposure to Fe, welding fumes, and quartz dust, as well as to asbestos and the solvent toluene.

In the working age group of 20-65 years, it was the same pattern as in the all ages (20+ years) group. However, among men exposure to ARHC, including toluene, the risk was significantly increased.

In the age group after retirement (66-75 years), less significant increased risks were found compared to the other two age groups. Though, significantly increased risks were still seen for both men and women exposed to CO, and Pb. Significantly elevated risks were also

observed for men exposed to diesel engine exhaust, and for women exposed to Fe, welding fumes, quartz dust, wood dust, and respirable dust.

Also in this study, the JEM (SWEJEM) was used to identify occupations with various particle/chemical exposures. Naturally, within some occupations, the workers are exposed to several particles/chemicals. Table 6 presents occupations with exposure (prevalence ≥ 50 % and all intensities) for the particles/chemicals with highest attributable fractions for first MI, i.e., diesel engine exhaust, CO, Fe, oil mist and welding fumes. As seen in this table, for example bus and tram drivers are exposed to both diesel engine exhaust and CO, and machine-tool operators are exposed to both oil mist and Fe. However, all occupations also have other particle/chemical exposures.

Table 6. Occupations with exposures to diesel engine exhaust, CO, Fe, oil mist, and welding fumes

Exposure	Occupation
Diesel engine exhaust	Bus and tram drivers
	Car, taxi, and van drivers
	Crop and animal producers
	Earth-moving- and related plant operators
	Field crop and vegetable growers
	Gardeners, parks, and grounds
	Heavy truck and lorry drivers
	Miners, shotfirers and quarry workers
	Motorized farm and forestry plant operators
	Railway brakers, signalers and shunters
	Salespersons, petrol stations
CO	Aircraft engine mechanics and fitters
	Blacksmiths, hammer-smiths, forging-press workers
	Bus and tram drivers
	Car, taxi, and van drivers
	Casters and coremakers
	Earth-moving- and related plant operators
	Fire-fighters
	Heavy truck and lorry drivers
	Lifting-truck operators
	Metal drawers and extruders
	Metal moulders
	Metal-heat-treating-plant operators
	Miners, shotfirers and quarry workers
	Motor vehicle mechanics and fitters
	Ore and metal furnace operators
	Ships´ engineers
	Transport laborers and freight handlers
	Welders and flamecutters
Fe	Aircraft engine mechanics and fitters
	Blacksmiths, hammer-smiths, forging-press workers
	Casters and coremakers
	Machine-tool operators
	Machine-tool setters and setter-operators
	Metal drawers and extruders
	Metal melters and rolling-mill operators
	Metal moulders
	Metal wheel-grinders, polishers, tool sharpeners
	Metal-heat-treating-plant operators
	Ore and metal furnace operators
	Plumbers
	Roofers
	Sheet-metal workers
	Structural-metal preparers and erectors

	Welders and flamecutters
Oil mist	Machine-tool operators
	Machine-tool setters and setter-operators
	Metal wheel-grinders, polishers, tool sharpeners
	Well drillers and borers and related workers
Welding fumes	Blacksmiths, hammer-smiths, forging-press workers
	Plumbers
	Welders and flamecutters

6 DISCUSSION

This thesis´ overall aim was to investigate occupational particle exposure in relation to COPD and CVD. To explore the relationships, different study designs were used: longitudinal (study I, part of study II, study III, and study IV) as well as cross-sectional (part of study II). Two of the studies were register-based (study I and IV) and two were field-studies (study II and III). The key findings of the respective studies and methodological considerations of the different studies and study designs are discussed below.

6.1 COPD STUDY – KEY FINDINGS

The findings in this study indicate that after adjusting for smoking, men occupationally exposed to any type of inorganic, organic, high levels to any combustion particles, and high levels of welding fumes had increased risk of developing COPD. More specifically, men exposed to RCS, gypsum and insulation, diesel exhaust, and high levels of welding fumes had higher risk. The risks were also higher, the higher exposure levels. These findings are consistent with earlier studies which provide some evidence for an association between the exposures and COPD (for example for RCS: (25, 83), for gypsum and insulation (84), for diesel exhaust (25, 85), for welding fumes (28, 86, 87)). Notably, in our study, increased risks were seen for exposure to RCS below the current European and Swedish OEL of 0.1 mg/m^3 (2004/37/EC), in our study average levels of 0.052 mg/m^3. Furthermore, there was a tendency of dose-response relationship among men exposed to particles of asphalt/bitumen. There are not many studies on asphalt particle exposure and COPD, and therefore our study adds new insight into this association including dose-response relationship. For women we saw an increased risk of COPD among those highly exposed to various organic particles from animal, flour, leather, plastic, soil, soot, and textile. Both men and women had increased risk if exposed to paper dust with an inverse dose-response relationship. An earlier study (88) indicates an association between paper dust exposure and impaired lung function. However, as the risk was higher in the low exposed groups it is possible that there are other exposures, prevalent within the occupations with paper dust exposure, which are affecting lung function.

Considering all occupational particle exposures included in this study, the PAFs in all ages were for men 10 % and women 3 % and combined for both gender 6 %. However, other studies have higher, around 15 %, estimates of PAF from exposures in working life. One explanation for our lower estimate is that we have only included exposure from certain particles, and not for example from gases irritating the airways. However, within our study we also identified occupations with exposures which are associated with increased risk of COPD as well as having a large proportion of COPD-cases such as welders and flamecutters, store and warehouse workers, or kitchen assistants and restaurant workers. These results would help identify where to put effort for reducing particle exposure.

6.2 CVD FIELD STUDY

6.2.1 Occupational particle exposure and common CVD biomarkers – key findings

The findings of the studied biomarkers indicate that the low to moderate occupational exposure to all types of particles (mean levels in all participants: respirable silica 0.027 mg/m^3, respirable dust 0.354 mg/m^3, PM 0.1-10 0.788 mg/m^3) included in this field study was associated with higher homocysteine levels, and lower HDL-levels. Significant, positive associations were found between exposure to both respirable dust and PM 0.1-10 and resting pulse rate. Also, a long-term (years) change with higher concentrations in LDL and homocysteine levels were found.

For homocysteine, also after adjusting for physical activity and alcohol consumption, both factors which might affect the levels of homocysteine (89, 90), there were only small effects on the results. Furthermore, there was no recovery seen during vacation, and long-term exposure showed increased levels for each year of occupational particle exposure, see Table 4 in section 5.2.2. Homocysteine levels that are increased have in earlier studies been linked to oxidative stress, induction of thrombosis, worsened functioning of the endothelium, but also to atherosclerosis and hypertension (91-93), thus our findings are noteworthy. Our results are also in line with a review from 2020 on particle exposure from ambient air and homocysteine (94), but contradictory to a later study on occupational welding fumes and homocysteine (95). Though, in this later study exposure measurement and biological sampling was not performed the same day. As we sampled the same day, our results might more accurately indicate the short-term effects of occupational particle exposure.

The levels of lipids in the blood are indicators of upcoming CVD. LDL is linked to atherosclerosis (96). However, HDL hinders the inflammation in the atherosclerosis process when there are high levels of LDL (97). The findings in our study indicated that respirable dust and PM 0.1-10 were associated with lower HDL-concentrations, which is supported by a study on ambient air where an association was found between PM 2.5 and PM 10 and lower HDL levels (98). However, in our study there was no change in HDL-levels after vacation nor was there any long-term change. The LDL-levels changed after an exposure-free period for all particle types, but the results also show an increased level for each year of occupational particle exposure. The lipid levels in the blood are affected by diet, but there were no differences in dietary habits between the high and low exposure groups. Also, physical activity (99) and alcohol intake (100) might affect the levels, but adjusting for these possible confounders did not affect the results to a large extent. In total, there seems to be an association between occupational particle exposure and LDL levels. Along with the long-term elevated LDL-levels, but unchanged HDL-levels, there is an increased risk of CVD.

Some of the studied other markers recovered during vacation when exposure was much lower, for example systolic and diastolic blood pressure decreased. However, it is also a

possibility that the blood pressure has decreased during vacation when the participants might have stressed less and or had more exercise (78, 101, 102). Elevated blood pressure is a pathway to CVD (46, 78), and earlier studies have shown an association between exposure to particles and blood pressure (79, 80).
In this study resting pulse rate was also associated with respirable dust and dust of PM 0.1-10. A high resting pulse rate is a risk factor for cardiovascular disease (81). After vacation all low-exposed groups had a higher and all high-exposed groups had a trend of lower resting pulse rate. Possibly, the measuring of pulse rate was different at worksites before vacation compared to the clinic after vacation due to the white coat syndrome, which is when the blood pressure of a participant is higher in a clinic when assessed by medical staff compared to own measurements (103). Also, it has been suggested that anxiety increases the blood pressure and pulse rate (103, 104). Furthermore, it is possible that the effect on pulse rate from particle exposure weakened during a period with less exposure (vacation) and stayed only in the group with high exposure. The effect being greater in the high-exposed groups is also in line with that there is an association between blood pressure and pulse rate (105).

Notably, also in this study, we saw these adverse effects on the CVD markers at exposure levels below the Swedish OELs for both respirable silica (RCS) of 0.1 mg/m^3 and respirable dust of 2.5 mg/m^3.

6.2.2 Occupational particle and noise exposure and short-term effects on pulse rate and blood pressure – key findings

In this study we found that exposure to particles of PM 0.1-10 in levels approximately above 0.5 mg/m^3 was significantly associated with elevated pulse rate within the same minute. A significant positive association with pulse rate was also found for noise exposure. As both particles and noise are prevalent at the working sites, we analyzed the joint effect on pulse rate and found an additive effect. Interestingly, the two types of exposures did not exist simultaneously to a large extent, the correlation coefficient between PM 0.1-10 and for example LAmax it was only 0.19, but this could be due to particles being logged every minute and noise every second.

Studies on joint occupational exposures of particles and noise and CVD outcomes are scarce. To our knowledge there is only one, which studied exposure to particles from diesel exhaust and noise, and their association with heart rate variability and endothelial function (106). Our study adds to the field of knowledge on joint occupational exposures.

In earlier studies, pulse rate has been associated with CVD and death (81). There is an association between pulse rate and peripheral blood pressure (105), which may explain the increased mortality (81, 107). There are also clinical and experimental studies which propose that a pulse rate that is sustained at a higher level, may play a part in the development of vascular disease (82). The higher pulse rate is probably linked to more exertion, and with more exertion also leading to more inhalation of particles (108). However, in this study the

mean physical workload was similar for the participants over their working day, indicating similar overall levels over the working day, and we did not have objective measurements during the day, and therefore we did not adjust for this.

Our results did not show any short-term associations between particle (or noise) exposure and blood pressure. It could be so that the timeframe is too short (seconds) between exposure of either particles or noise occurring and an effect on blood pressure. There were also few observations of blood pressure due to problems with the technical equipment. The equipment used was not suitable for reading blood pressure in real life working situations with participants moving.

6.3 CVD EPIDEMIOLOGICAL STUDY – KEY FINDINGS

In both analyses of cumulative and recent exposure for both sexes, there were several particles/chemicals significantly associated with increased risk of first MI after adjustment for other occupational exposures of lack of decision authority, physical workload, noise, and for some particles/chemicals also other particles/chemicals. More specifically, for the whole study population *both cumulative* exposure in all ages (20+ years) *and recent exposure* to the combustion compounds diesel engine exhaust, PAH including BAP, and SO2, the gases CO and volatile sulfur compounds, and the metals Cd and Fe were significantly associated with first MI. Additionally, in all ages (20+ years) in the whole study population, cumulative exposure to the combustion compounds gasoline engine exhaust, the metals Cr and Pb, as well as to oil mist, benzene, gasoline, pulp or paper dust, and respirable dust was also significantly associated with first MI. A near significant association was found for welding fumes and quartz dust. Exposure one year prior MI to formaldehyde, welding fumes, asbestos, and flour dust was also significantly associated with MI in the whole study population. The risk estimates changed very little when adjusting also for life-style factors of smoking and BMI as well as stratifying on educational level. Furthermore, there would have been approximately 3,300 first MIs prevented with no occupational exposure to the five particle types of diesel engine exhaust, CO, Fe, oil mist, and welding fumes only. Taken together, these findings indicate that occupational particle exposure needs to be considered when evaluating risk of first MI.

Several of the findings in this study are line with earlier research results on particle exposure and ischemic heart disease including MI. However, in this study we also adjusted for joint occupational exposures, hence strengthening the associations of a true effect from particles. *Combustion compounds* have in a systematic review (2010) been associated with ischemic heart disease (66), and a Swedish study (2014) found an association between motor exhaust and MI (109). A recent (2022) review concluded that more evidence is warranted for establishing if there is an association between PAH and MI (110), although there are clinical findings suggesting PAH triggers CVD, and that an inflammatory atherosclerotic plaque is induced from PAH-exposure (111, 112).

An association between *the gas* CO and MI have been found in a systematic review on ambient air (113), but our results support an association also in occupational settings where the levels often are much higher than in ambient air.
The *irritant* oil mist is not that much studied, but oil-based fluid-exposure have been found to increase the IHD-risk (114, 115).
Welding fumes-exposure was associated with slightly higher risk of MI in a systematic review from 2015 (65).
The *inorganic* fibres of asbestos are established to have an association with ischemic heart disease (116), and quartz particles to have an association with MI (60, 117).

This study also adds new knowledge on occupational particle exposure and risk of first MI. Exposure to *gases* of volatile sulfur compounds both cumulative and recent exposure was in our study associated with an elevated risk of first MI, an association not studied before as far as I know. Also, findings from this study show significant associations between first MI and cumulative exposure to the *metals* Cd, Cr, Fe, and Pb. Earlier studies only imply associations between Pb and Cd-exposure and atherosclerotic disease (118, 119), and insufficient or low evidence of an association between Cr and Fe (120, 121). Furthermore, to my knowledge there are no previous studies on the organic particles included in this study and incidence of first MI.

6.4 METHODOLOGICAL CONSIDERATIONS

The results from studies always need to be interpreted in view of the methodological issues of each study and its design. Below is an attempt to discuss the study designs used in this thesis as well as strengths and weaknesses of each study.

In observational studies such as register-based studies, the type we conducted in study I and IV, the accuracy of the results depends on the degree of random errors and systematic errors. However, errors should also be considered in the field studies, in this thesis study II and III.

6.4.1 Random errors

Random errors are due to variability within the data and affect the precision, or reliability of the study. This problem is often solved by using bigger samples sizes. Both study I, and especially study IV had large sizes, and study III had many observational points of both particle exposures and pulse rate, which minimized the risk of chance findings and random errors due to variability in the data. However, in study II, the smaller sample size could lead to random errors. However, this is also reflected in broad confidence intervals in the results, and thereby considered in the interpretations.

6.4.2 Systematic errors

Errors or biases that are consistent and repeated and associated with the design or collection of data are called systematic errors. Systematic errors lead to lower validity, i.e., that there is systematic and non-random discrepancy between the observed effect and the true effect. These errors could be referred to as either selection bias, information bias, or confounding.

Selection bias refers to errors that occur if subjects are selected for a study, or the subjects' participations in a study, is influenced by the outcome and the exposure. This type of error often occurs in retrospective case-control studies where both cases and controls volunteer participation. Also, in these studies, both the exposure and outcome already have occurred. In study I we defined subjects as having COPD partly from questionnaire data with subjects themselves answering a question if they had been diagnosed with COPD by a physician. It is not likely that they reported a COPD-diagnosis but not having it due to the stigma of the disease, but more likely that they had not understood or forgotten or denied the COPD-diagnosis. This led to rare false positives but some false negative cases. Therefore, reporting in the surveys not covering most/all COPD-diagnosis led to the estimated risks having lower precision, but these risk estimates are probably not systematically biased. Though, maybe one could argue that those answering the surveys are healthier than the general population.
Study II and study III are based on the same population. There is a possibility that we did not include subjects who already had some CVD, i.e., we included a healthier population than the overall occupational population. This selection bias is called healthy worker effect, see also 6.4.4. under Limitations.
In study IV we based our cohort on all individuals working in Sweden, hence there is no systematic error due to selection bias. Though, it might be some individuals not caught in the analyses due to the registers not having information about occupations for certain periods (the years between the censuses, and 1990-2001), about some self-employed, and for some occupations. However, in the analyses we have imputed information from the individuals' occupational anamneses the surrounding years.

Information bias could occur if the collected information about or from the participants are categorized incorrect and thereby misclassified. The misclassification can be either *differential* (if the exposure classification differs between cases and non-cases or if the outcome classification differs between the exposed and unexposed) or *non-differential* (if the classification of exposure does not differ between cases and non-cases or the classification of outcome does not differ between unexposed and exposed). When using JEMs, as we did in study I and IV, all subjects within the same occupation are assigned the same exposure-level of particle-concentration. Naturally, this is not true due to different work tasks etc. In study I on COPD and IV on MI when using JEMs we assigned the group-level exposure concentrations on the single individuals hence introducing misclassification of exposure to the participants. Furthermore, applying on men and women respectively, the JEM used in study I on COPD as well as the JEM used for particles in study IV, were not sex-specific and based on personal exposure measurements on men, not women. Ideally, occupational exposure levels for the different sexes would have been used in the analyses, if available.

However, as the exposure classification does not differ between cases and non-cases in either of the studies, the misclassification of exposure is non-differential and the results are most likely attenuated, in these studies HRs towards 1.00. Though, one should also keep in mind that when using JEMs there might not be any biased HRs, but only a loss in precision (Berkson error) (122).

Confounding is a bias which arises when groups are compared, for example exposed and non-exposed. A confounder-variable is associated with both exposure and outcome, and if not considered the confounders can lead to either an overestimation or an underestimation of the true effect. Therefore, confounders are adjusted for in the statistical analyses.
In study I on COPD, as mentioned above, we adjusted for the potential confounder smoking. In this study education was used as a proxy for socioeconomic position, which is associated with factors and exposures in lifestyle, for example smoking. However, education and occupation are closely correlated. Therefore, if adjusting for education one might over-adjust, and education was not included in the main analyses.
In both study II and III we considered confounding from sex and smoking, by only including non-smoking male workers. In study II we also adjusted for variables which differed between the groups, i.e., alcohol consumption, and physical activity.
In study IV on MI we adjusted for potential confounders from other occupational exposures of lack of decision authority, physical workload, noise, and particles/chemicals. Furthermore, we adjusted for life-style factors of smoking and BMI, and as a proxy for socioeconomic confounding we used education.

6.4.3 COPD-study

Strengths

The COPD study (study I) is a population-based prospective longitudinal cohort-study, a study-design which is superior when studying outcomes that have long periods of development, such as COPD. All subjects were disease-free at baseline in 1990 when we collected information about the exposure, which enabled us to ensure that exposure occurred prior to COPD. This is crucial when trying to establish associations between exposure and outcome as well as causality.

The subjects were followed for a maximum of 24 years (1990-2014). The large sample size of 43,641 subjects and the long time the cohort was followed was a strength. In epidemiological studies it is important to have data on possible confounders. When adjusting for these a better comprehension of the true association between the exposure of interest in the study and the outcome is achieved. In this study the use of individual data was a clear strength allowing us to adjust for relevant confounders such as smoking. We also used register data in a JEM when assessing the exposure which is objective and transparent allowing for results to be replicated.

Limitations

Developing COPD usually takes decades of time. This study used exposure data from the occupation each individual had only in 1990, but we don't have any information about the duration of exposure and the later exposure levels. The subjects may have changed occupations during the follow-up period (as latest year 2014), or the exposure levels within an occupation may have changed over time. In a study from 2022 of workers in Sweden, Gustavsson et al, observed an overall drop in exposure levels, especially between 1980 and 2001, for some of the particles associated with increased risk of COPD in this study; RCS, diesel exhaust, and welding fumes (11). However, if the exposure levels have been over-estimated, than the risks have been underestimated (123).

In this study it was not possible to separately analyze the combustion particles from fire smoke, environmental tobacco smoke, and plastic smoke. This is due to how the JEM is constructed. In our study we also combined exposure of soil, leather, plastic, soot, animal, textile, and flour, otherwise the exposed subjects would have been too few in each category of organic dust. Previous studies have indicated weak associations with COPD for example for dust in animal farming (124), and occupational environmental tobacco smoke exposure (125).

Another limitation in this study is that we did not have the ability to use data of COPD-diagnosis according to the GOLD-criteria, but it is likely that most physician-diagnosed cases had a diagnosis which was based on these criteria. Furthermore, receiving drugs which at that time were specific for COPD, added more cases to the study as well as increased the likelihood that the diagnosis was based on the GOLD-criteria.

Generalizability

A study's internal validity depends on the systematic errors, with few systematic errors increasing the internal validity. External validity, also called generalizability, indicates how well the findings in a study could be generalized to other populations. The COPD-study is based on a population within Stockholm County where the proportion of white-collar workers are high compared to Sweden as a whole, and therefore the results is representative for a Swedish urban population. Within the studied occupations the exposures can differ substantially in other countries, for example due to other settings, working hours, and use of personal protections, and the generalizability is lower to countries other than Sweden.

6.4.4 Occupational particle exposure and common CVD markers

Strengths

A major strength of this study, study II, was that we performed 6-8 h of individual sampling of the exposures. We also performed biological sampling the same day of exposure, and directly after vacation giving us longitudinal data of the outcomes, strengthening the findings.

Furthermore, we handled the biological samples in a homogeneous way. We also randomized all the samples before analyzing them in the same batches. This minimized bias from technical or batch effects. Another strength is that we only included non-smoking men, which minimized effects from sex- and smoking confounding.

Limitations

The small number of participants was a limitation, and statistical power could have been affected. Also, only one day of exposure measurements was a limitation since it reflects the particle exposure for each participant that day. However, quantitative measurements of both particle exposures and markers of CVD allowed us to create high- and low exposed groups with sufficiently many workers in each group to have as much statistical power as possible. Furthermore, we did not know anything about those who have quit their job, which could be due to health problems. This bias (healthy worker survivor effect) indicating that only those healthy enough remain in their occupation. The bias could infer lower associations between the particle exposures and the markers, and the associations being underestimated.

Other thoughts

The first part of this study is cross-sectional which limits the interpretation regarding causality. We don't know if the exposure is prior outcome or if the biomarker levels are due to something else than occupational exposures. However, in the second part of the study we also conducted biological sampling longitudinally for every participant investigating recovery effects of biomarkers indicating the role of particle exposure on the levels of biomarkers.

6.4.5 Occupational particle and noise exposure and short-term effects on pulse rate and blood pressure

Strengths

The major strength of this study, study III, was that we measured the exposures of particles and noise, and the outcomes pulse rate and blood pressure continuously and simultaneously. The measurement devices were carried by the participants themselves providing objective and transparent measurements. As this study is based on the same study population as in study II, i.e., non-smoking men, we minimized confounding effects from sex and smoking.

Limitations

The major limitation of this study is that we don't have any equipment-based logged information about the participants exertion during the working day. As we don't have second/minute information about this co-variate we were not able to adjust for this. Another limitation is that we were not able to measure blood pressure at workers who were moving and performing their work. This require equipment which is stable and accurate for these types of situations.

6.4.6 CVD epidemiological study

Strengths

This prospective, longitudinal population-based study is very large which is a clear strength. The large size including million individuals enabled us to perform sex-specific analyses and to adjust for other occupational exposures than particle/chemical exposure which are possible confounding factors. We were able to adjust for exposures of lack of decision authority, physical workload, noise, and for particles/chemicals of interest on confounding particles/chemicals on occupational level, but also individual risk factors of smoking and BMI. Also, the large size enabled stratified analyses on low level education.

Limitations

The individual risk factors of smoking and BMI were derived from the subsets, sometimes several years prior the year of exposure/occupational code. We then used this data assuming that smoking and BMI are constant for the following years. However, earlier research has indicated that individuals start smoking when they are young, and not older (126). Therefore, data of smoking from when women had a baby, and men when they enrolled for military service, ought to be valid. The data on BMI, however, may vary over the years, and we have only included data from one occasion, which is a limitation.

Generalizability

This study is based on the general adult working population and not limited to any specific region in Sweden, hence it is generalizable to the working population of Sweden and other countries with similar occupational exposures and settings, working hours etc. as Sweden, like the Nordic countries.

Other thoughts

The results in the whole study population, both from recent and cumulative exposure, are more similar to the results in men than in women. This has to do with more cases over the years among men, and also more men being exposed. Fewer cases and fewer exposed among women do not affect the results of the whole study population that much. For example, for cumulative exposure of diesel engine exhaust, the risk estimate for the whole study population of 22,624 cases being HR 1.60 (CI 1.45-1.77), for men with 21,641 cases a HR of 1.84 (CI 1.66-2.04), and for women with only 983 cases a HR 1.40 (CI 0.85-2.32). Results based on few cases in one of the sexes should be interpreted with caution. For example, for MMMF significant results were seen among women (HR 1.42 CI 1.08-1.86), but the number of cases over the entire study period of 32 years is only 50. The male risk estimate (HR 0.96 CI 0.95-0.97) with 10,401 cases should be considered more reliable.
For some of the results in the recent exposure-analyses, the HR of the whole population is not between the levels of HRs of men and women, respectively. For example, this can be seen for volatile sulfur compounds where the adjusted HRs are 1.10 (CI 1.03-1.18) of the whole population, 1.06 (CI 0.99-1.14) for men, and 0.95 (CI 0.72-1.26) for women. These findings

are due to the median for the respective particle/chemical exposure within the whole population is different from the median for men, which is also different for the median for women. Furthermore, when combining exposure groups of men and women, and setting a new cut-off for median in the whole population, some occupational groups could change "side" (for example from being above in the sex-specific analyses to below the median in the whole population-analyses). What was a dose-response in the sex-specific analyses, can then be a reversed trend in the combined whole population-analyses. This is known as Simpson´s paradox (127). However, in this study, when comparing the results, it is better do so with the crude results as the confounders also affect the results. For volatile sulfur compounds, the crude HRs are 1.27 (CI 1.19-1.35) of the whole population, 1.25 (CI 1.17-1.33) for men, and 1.45 (CI 1.13-1.86) for women. For better understanding and interpretating the results, and for better avoiding Simpson's paradox the same cut-off levels/medians for each respective particle/chemical should be chosen for the whole study population, men, and women.

In this study, we performed analyses of exposure one year prior first MI. One might wonder if exposure one year prior first MI is long enough. The induction time may be longer given that MI is often caused by an atherosclerosis. Maybe the exposure one year prior first MI could also reflect a longer period, for example 5 years. We don't know this, as we have not calculated the effect for various time intervals.

6.5 GENERAL DISCUSSION ON OCCUPATIONAL PARTICLE EXPOSURE IN RELATION TO COPD AND CVD

In this thesis there are some particle types which show effect on the outcomes in two or more of the included studies, i.e., diesel engine exhaust, welding fumes, and respirable particles/silica which all are associated with both COPD and CVD. Worth noting, is that exposure to diesel engine exhaust, welding fumes, and respirable crystalline silica are also associated with lung cancer (128-130), thus particles of concern.

Diesel engine exhaust was associated with both incident COPD and first MI. A borderline significant association with COPD with a positive dose-response relationship was found for men in study I, and a clear association with MI in the whole study population in all age groups (20+ years, 20-65 years, 66-75 years) cumulatively exposed in study IV.

Welding fumes was associated with both incident COPD and first MI in study I and IV, respectively. In study I there was a near significant association with COPD among men with indications of a positive dose-response relationship after adjusting for smoking. In study IV we found near significant associations for the whole study population of all ages (20+ years) cumulatively exposed to welding fumes, and significant associations in the working ages of 20-65 years. A dose-response relationship was also indicated in recent exposure in the whole study population.

Respirable particles were associated with the studied outcomes in all of the studies including this size-fraction, namely study I, II and IV. In study I, a significant association was found among men between respirable crystalline silica and incidence of COPD, but also among

men high exposed to welding fumes and Fe, measured as the respirable fraction of particles, and COPD-incidence. In study IV, an increased risk of first MI was found in the whole study population after cumulative exposure to respirable particles, and after exposure one year prior MI there was an indication of a dose-response association. The adverse CVD-effects of respirable particles found in study IV are supported by the findings in study II. In this study, an indication of an association between respirable silica and respirable dust overall and lower HDL concentrations in blood and a higher resting pulse rate was found. Furthermore, in this study, after an exposure-free period during vacation, both systolic and diastolic blood pressure and LDL concentration was significantly reduced.

Earlier studies on COPD and CVD have come to the same conclusion (25, 28, 60, 65, 109, 131), but interestingly in this thesis is that we, specifically in the CVD-analyses, assessed and adjusted for other occupational joint exposures as well. This is a major strength when it comes to evaluating the importance of occupational particle exposure in relation to incidence of CVD. In study II and III, we considered exposures such as diesel fumes, welding fumes, and noise. In study IV we adjusted for the psychosocial factor of lack of decision authority, physical workload, and noise. Even after inclusion of these concurrent exposures, these particle types are of special concern. Furthermore, there are occupations where several of the studied occupational particle exposures are present, thus affecting the workers heavily, for example within construction industry, mining, transport sector, and the agricultural sector.

In earlier studies an association between occupational exposure to respirable silica and asbestos and cor pulmonale have been found (54). Cor pulmonale is when there is a change in structure and function of the heart's right ventricular, caused by an illness primarily in found in the respiratory system. The most common cause of cor pulmonale is COPD (132), but also fibrosis in the lung (133). The latter caused for example by respirable silica, or asbestos fibres. An important mechanism is thought to be strain on the heart's right ventricular due to an elevated pressure in the pulmonary circulation (54). In this thesis systolic blood pressure was reduced after vacation among workers high exposed to respirable silica and respirable particles overall (study II). Furthermore, an association was found for respirable silica and asbestos fibres with both COPD and first MI (study IV). These findings support earlier studies on an association between respirable silica and asbestos fibres and cor pulmonale.

The findings in this thesis are interesting since some exposure levels of different particles remain at approximately similar levels as in 2001. An earlier study has found that in Sweden the exposure levels of respirable crystalline silica (RCS) and welding fumes have remained approximately the same since 2001, and the exposure levels of diesel engine exhaust have constantly decreased. The proportions exposed to these three agents are approximately the same. However, in the older age-group of worker ≥ 55 years of age the proportions exposed to welding fumes and diesel engine exhaust have increased, and to RCS remained approximately at the same level, between 2001 and 2013 (11).

In our study I, the PAF for COPD from occupational particle exposure was among men in all ages 10 % and slightly higher in working ages up to 65 years of age. Earlier studies have

estimates of around 15 % of PAF from occupational exposures. The higher number could be due to them including other occupational exposures than particles. Also, as smoking decreases, the importance of other exposures would increase. The same would go for various CVD, for example MI.

As the population is ageing the working life is expanding. In Sweden, the pension regulations changed in 2020 and workers' right for state pension was increased from 61 to 62 years of age as well as the right for not having to retire from 67 to 68 years of age (134). There are also increases planned stepwise for the years 2023 and 2026. The right for receiving disability pension is also strict due to the changes in the pension system which aim is to make people work longer. However, for those workers with poor health, these new levels and regulations may be troublesome as they might not cope with working in higher ages (135).
As argued from results of the included studies, exposure to particles increase the risk of incident COPD and CVD. Thus, by preventing poor health by improving work environment, for example by reducing occupational exposure to particles, the likelihood of people remaining longer at work will increase. Reducing particle exposure levels at work would prevent incident COPD and CVD, and one tool of making this happen is to reduce OELs for particles.

7 CONCLUSIONS

This thesis contributes to state-of-the-art knowledge on occupational particle exposure and its relation to COPD and CVD, the last outcome with a focus on early biomarkers and with first MI.

The results from study I on COPD indicate that there are smoking-adjusted increased risks after exposure to various types of particles, and that there were sex-differences. Men had higher risk with dose-response relationships if exposed to RCS, particles of gypsum and insulation, diesel engine exhaust, and welding fumes, as well as a tendency of a dose-response relationship of particles of asphalt/bitumen. Notably, the increased risks were seen in levels of exposure below the current European and Swedish OEL for RCS of 0.1 mg/m^3. Women had increased risks if exposed in higher levels to organic particles from animal, flour, leather, plastic, soil, soot, and textile. The population attributable fraction (PAF) from inorganic, organic, and combustion particles, and welding fumes was 9.9 % among men and 2.8 % among women in all ages.

In study II low to median exposure levels of respirable silica (RCS), respirable dust, and PM 0.1-10 was associated with changes in biomarkers which are indicators of adverse health effects, all which may cause CVD. Also, within this study, the effects were seen below the OELs of RCS of 0.1 mg/m^3 and respirable dust of 2.5 mg/m^3. Also, long-term. i.e., years, of exposure of particles in dust-exposed jobs was associated with adverse effects. In study III we also found that particles of PM 0.1-10 were associated with elevated pulse rate the same minute, and there was an additive effect with noise.

The study on first MI, study IV, found that that several particles and chemicals were associated with first MI even after adjustments for the concurrent occupational exposures of lack of decision authority, physical workload, noise, and other particles/chemicals. Individual risk factors of smoking and BMI, and education as a proxy for socioeconomic conditions did not change the results to a large extent. These associations were backed by trends in cumulative exposure. Furthermore, if occupational exposure to diesel engine exhaust, CO, iron, oil mist, and welding fumes had not existed, approximately 3,300 first MIs would have been prevented.

Overall, the findings in this thesis indicate an association between occupational particle exposure and incident COPD as well as first MI, with changes of biomarkers to support adverse effects in the body which might result in various CVDs. Notably, these adverse health effects were seen at exposure levels below current OELs of RCS and respirable inorganic dust.

8 POINTS OF PERSPECTIVE

However, though each of the four studies included in this thesis has significant results of associations between different occupational particle exposures and the outcomes, one should keep in mind that these results are pieces in a puzzle for establishing causal relationships. Each of the included studies all have their strengths and weaknesses.

Both in study I and IV the analyses used JEMs which were based on sampling on men. In order to have more accurate risk estimates on women regarding incident COPD and first MI, the ideal would be to use JEMs based on measurements on women.

As we did in study IV, when we adjusted for other occupational risk factors, future studies on the relationship between occupational particle exposure and COPD should adjust for other occupational risk factors as well. It would also be interesting to include observations of exposure levels for several years.

In study III on short-term associations, we did not find any association between either particle or noise exposure and blood pressure. This is mostly likely due to technical measurement problems. In future studies, to be able to analyze these relationships, a well-functioning equipment which allows people to move around at work and at the same time provide stable monitoring of the blood pressure is crucial. Including more study participants would increase power, and thereby also finer analyze the interaction between particle and noise exposure. This study found short-term significant relationships with occupational particle and noise exposure and pulse rate. However, as pulse rate is related to physical activity, future studies should also include simultaneous, continuous measurements of exertion, so that this covariate can be included in the analyses.

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11 SUPPLEMENTARY MATERIAL

Supplementary table 1. Dose-response relationships among men and women for incidence of COPD based on occupational particle-exposure. Hazard ratios (HR) with 95% confidence interval (CI) after adjustment for smoking. [NA = not applicable]. (Study I)

		Men		*n*	*n*				Women		*n*	*n*			
Agent	**Dose**	**Cut-off [a] mg/m³**	**Mean mg/m³**	**No COPD**	**COPD**	**HR [b]**	**95 % CI**	**p-value [c]**	**Cut-off [a] mg/m³**	**Mean mg/m³**	**No COPD**	**COPD**	**HR [b]**	**95 % CI**	**p-value [c]**
Any inorganic particles	*All*	NA		2005	135	**1.39**	**1.15-1.67**	NA	NA		89	9	1.85	0.96-3.57	NA
	Low		0.058	986	55	1.24	0.94-1.63	**0.001**		0.079	49	6	2.21	0.99-4.93	0.097
	High	≥0.125	0.248	1019	79	**1.51**	**1.20-1.90**		>0.125	0.346	40	3	-	-	
RCS [d]	*All*	NA		881	61	**1.46**	**1.13-1.90**	NA	NA		18	3	-	-	NA
	Low		0.013	434	25	1.28	0.86-1.90	**0.016**		0.011	8	1	-	-	0.991
	High	≥0.048	0.052	447	36	**1.63**	**1.17-2.27**		≥0.017	0.057	10	2	-	-	
Iron dust	*All*	NA		945	60	1.21	0.93-1.58	NA	NA		69	6	1.58	0.71-3.53	NA
	Low		0.053	458	19	0.86	0.55-1.36	**0.048**		0.105	31	3	-	-	0.083
	High	≥0.125	0.309	487	41	**1.49**	**1.09-2.04**		>0.140	0.345	38	3	-	-	
Other inorganic particles and fibres [e]	*All*	NA		737	54	**1.56**	**1.18-2.05**	NA	NA		7	0	NA	NA	NA
	Low		0.075	176	12	1.56	0.88-2.75	**0.002**		0.075	5	0	NA	NA	0.976
	High	≥0.113	0.163	561	42	**1.56**	**1.15-2.13**		>0.075	0.186	2	0	NA	NA	
Any organic particles	*All*	NA		2896	176	**1.33**	**1.12-1.56**	NA	NA		1806	122	**1.22**	**1.01-1.47**	NA
	Low		0.054	1686	111	**1.44**	**1.18-1.76**	0.227	≥0.050	0.025	880	53	1.15	0.87-1.52	0.190
	High	>0.080	0.620	1210	65	1.17	0.90-1.50			0.292	926	69	**1.28**	**1.01-1.64**	
Wood dust	*All*	NA		570	31	1.26	0.88-1.81	NA	NA		254	6	0.53	0.24-1.19	NA
	Low		0.037	118	5	-	-	0.751		0.026	243	6	0.60	0.27-1.33	0.112
	High	≥0.475	0.557	452	26	1.27	0.86-1.87		>0.026	0.295	11	0	NA	NA	
Paper dust	*All*	NA		573	39	**1.39**	**1.01-1.93**	NA	NA		312	29	**1.56**	**1.08-2.25**	NA

	Low		0.032	243	21	**1.78**	**1.15-2.74**	0.394		0.038	144	18	**1.81**	**1.14-2.89**	0.212
	High	≥0.080	0.104	330	18	1.11	0.70-1.78		≥0.080	0.097	168	11	1.27	0.70-2.29	
Oil mist	*All*	NA		653	41	1.20	0.88-1.64	NA	NA		31	2	-	-	NA
	Low		0.041	358	17	0.95	0.59-1.54	0.742		0.033	17	1	-	-	0.787
	High	>0.044	0.664	295	24	1.47	0.98-2.21		>0.044	1.173	14	1	-	-	
Cooking fumes	*All*	NA		104	9	**2.21**	**1.14-4.27**	NA	NA		524	30	1.01	0.70-1.45	NA
	Low		0.015	48	4	-	-	0.039		0.015	368	19	0.87	0.55-1.37	0.566
	High	≥0.038	0.038	56	5	-	-		>0.015	0.038	156	11	1.39	0.77-2.51	
Other organic particles [f]	*All*	NA		1136	64	1.23	0.95-1.59	NA	NA		930	61	1.21	0.94-1.57	NA
	Low		0.048	475	27	1.19	0.81-1.75	0.206		0.032	383	11	0.62	0.34-1.13	0.218
	High	≥0.080	0.455	661	37	1.26	0.91-1.75		≥0.285	0.399	547	50	**1.53**	**1.15-2.04**	
Any combustion particles	*All*	NA		2813	167	1.17	0.99-1.38	NA	NA		855	49	1.07	0.80-1.42	NA
	Low		0.023	1542	79	1.09	0.86-1.37	0.710		0.010	438	21	0.85	0.55-1.31	0.967
	High	>0.049	0.235	1271	88	**1.25**	**1.00-1.56**		>0.012	0.088	417	28	1.32	0.91-1.92	
Asphalt/bitumen particles	*All*	NA		251	22	1.39	0.91-2.12	NA	NA		3	0	NA	NA	NA
	Low		0.009	67	5			0.214		0.009	1	0	NA	NA	NA
	High	≥0.025	0.038	184	17	**1.71**	**1.06-2.76**		≥0.025	0.044	2	0	NA	NA	
Diesel exhaust	*All*	NA		2305	139	1.18	0.99-1.41	NA	NA		232	15	1.15	0.69-1.92	NA
	Low		0.016	1129	59	1.11	0.85-1.45	**0.019**		0.015	120	7	1.09	0.52-2.29	0.803
	High	≥0.030	0.078	1176	80	1.24	0.98-1.56		>0.030	0.068	112	8	1.21	0.61-2.44	
PAH (µg/m^3) [g]	*All*	NA		843	51	1.10	0.83-1.46	NA	NA		30	2	1.36	0.34-5.42	-
	Low		0.045	413	34	1.35	0.95-1.90	0.585		0.023	13	1	-	-	0.864
	High	≥0.093	0.396	430	17	0.81	0.50-1.31		≥0.090	0.725	17	1	-	-	
Other combustion particles [h]	*All*	NA		275	10	0.82	0.44-1.53	NA	NA		603	32	1.00	0.70-1.42	NA
	Low		0.027	109	6	1.37	0.61-3.06	0.189		0.010	368	19	0.87	0.55-1.37	0.351
	High	≥0.095	0.188	166	4	-	-		>0.010	0.067	235	13	1.29	0.75-2.23	

Welding fumes	*All*	NA		955	61	1.22	0.94-1.58	NA	NA		69	6	1.58	0.71-3.53	NA
	Low		0.077	535	26	0.94	0.63-1.39	0.067		0.074	45	4	-	-	0.074
	High	>0.090	0.805	420	35	**1.57**	**1.12-2.21**		>0.090	1.089	24	2	-	-	

[a] The cut-off level between low and high exposure is based on the geometric mean of exposure for each particle/group of particles

[b] Adjusted (age as a categorical variable, smoking as smoking status (ever vs never smokers) and number of packyears). The reference for each agent was those unexposed to the agent.

[c] Trend test including the unexposed

[d] Respirable crystalline silica

[e] Particles from gypsum and insulation material

[f] Particles from soil, leather, plastic, soot, animal, textile, flour

[g] Polycyclic aromatic hydrocarbons

[h] Particles from environmental tobacco smoke, plastic smoke, fire smoke