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# Environmental Exposures and Cardiovascular Disease

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## Preface

This report summarizes current knowledge about how environmental exposures, including exposures in the work environment, may contribute to cause cardiovascular disease (CVD). Despite a decreased incidence of CVD in recent decades, in Sweden and most other countries, this group of diseases remains a major cause of morbidity and mortality. Because environmental exposures are often modifiable, knowledge about their role in CVD aetiology forms important basis for the development of preventive strategies.

Human environment is complex and by no means this report is aimed at providing a comprehensive overview of all environmental exposures of potential relevance for CVD aetiology. The selection of exposure factors to address was made based on current public and professional concerns for exposure-related CVD as well as front line research activities among scientists at the Institute of environmental medicine (IMM). IMM is a department at Karolinska Institutet and an interdisciplinary research institution within the broad field of environmental medicine. IMM conducts research within the areas of environmental and occupational medicine, toxicology, physiology, epidemiology, and biostatistics with the aim to clarify how environmental and lifestyle factors affect our health and which role genes have. IMM also serves as a scientific advisor to public authorities within the area of environmental medicine.

Several researchers at the IMM contributed to this report which is a collaborative effort. Associate Professor Karin Leander coordinated the work. Exposure factors in the general surrounding are addressed, including air pollution, noise, urban green structures, and climate related heatwaves. Further, diet and certain contaminants are addressed, as well as selected occupational chemical exposures and occupational noise. Furthermore, the report summarizes evidence of associated biological mechanisms involved in CVD development. In each chapter, the authors discuss potential openings for further research in this field. The report also includes a concluding chapter where these research needs are summarized.

## Förord

Denna rapport sammanfattar aktuell kunskap om hur miljöfaktorer, inkluderande faktorer i arbetsmiljön, kan bidra till att orsaka kardiovaskulär sjukdom. Trots en minskande incidens av kardiovaskulär sjukdom under de senaste årtiondena, i Sverige såväl som i de flesta andra länder, är denna grupp av sjukdomar fortfarande en av de främsta orsakerna till sjuklighet och död. Eftersom exponeringsfaktorer i miljön ofta går att påverka utgör kunskap om deras roll i sjukdomsetiologin en viktig grund för utvecklingen av förebyggande strategier. En svensk sammanfattning av rapporten återfinns på sidan 158.

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# 1. Introduction

## Cardiovascular diseases

Cardiovascular disease (CVD) is a large group of diseases, many of which are related to atherosclerosis, a systemic inflammatory disorder of the vessel wall, which causes impaired blood circulation and ischemia. Among the CVDs, coronary heart disease (CHD), alternatively termed coronary artery disease (CAD) or ischemic heart disease (IHD), is one of the major groups of diagnoses with myocardial infarction (MI) being the most common single diagnosis. Another major group of CVD diagnoses is stroke. The vast majority of the strokes are ischemic, as opposed to haemorrhagic. Whereas CHD, stroke and many other CVDs including peripheral artery disease (PAD) and aortic disease most often are atherosclerosis related, other common diagnoses including cardiac arrhythmia, heart failure, and cardiomyopathy have less clear connection to atherosclerosis.

The International Statistical Classification of Diseases and Related Health Problems (ICD), version 10, groups diseases of the circulatory system into one chapter: Chapter IX. It covers diseases with codes from I00–I99, as shown in Table 1. The ICD is a tool for reporting and grouping conditions and factors that influence health and has become the international standard diagnostic classification system for all general epidemiological and many health management purposes.

Table 1. Grouping of cardiovascular diseases and conditions in the International Statistical Classification of Diseases and Related Health Problems (ICD), version 10.

ICD code	Group of diseases
I00–I99	Diseases of the circulatory system
I00–I02	Acute rheumatic fever
I05–I09	Chronic rheumatic heart diseases
I10–I15	Hypertensive diseases
I20–I25	Ischaemic heart diseases
I26–I28	Pulmonary heart disease and diseases of pulmonary circulation
I30–I52	Other forms of heart disease
I60–I69	Cerebrovascular diseases
I70–I79	Diseases of arteries, arterioles and capillaries
I80–I89	Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified
I95–I99	Other and unspecified disorders of the circulatory system

## Burden of cardiovascular morbidity and mortality globally and in Sweden

Despite a declining trend in incidence over several decades, CVD is a major cause of health loss for all regions in the world (Roth et al. 2017). Between 1990 and 2015 CVD mortality decreased sharply in all high income countries and in some middle countries, whereas in low income countries it decreased only gradually or not at all (Roth et al. 2017). In many regions where CVD mortality declined, there are now indications of plateauing or upward trends (Roth et al. 2017) (Shah et al. 2019).

As compared to other European countries, in 2013 Sweden had an intermediate burden of CVD (Townsend et al. 2016). CVD is the leading cause of death in Sweden and accounted for about 34 % of all deaths in 2017 (National Board of Health and Welfare, 2018a). During the period 2003-2013, the CVD age-standardized mortality rate decreased by 31 % in men and 26 % in women (Townsend et al. 2016).

The yearly number of MI among Swedish inhabitants is about 26,000, and so is the number of stroke occurrences (National Board of Health and Welfare 2018b and 2018c). For both these diseases, the incidence increases by age and is higher for men than women in all age groups as shown in Figure 1 and Figure 2 where data are from 2016. The difference by sex is however more pronounced for MI than for stroke.

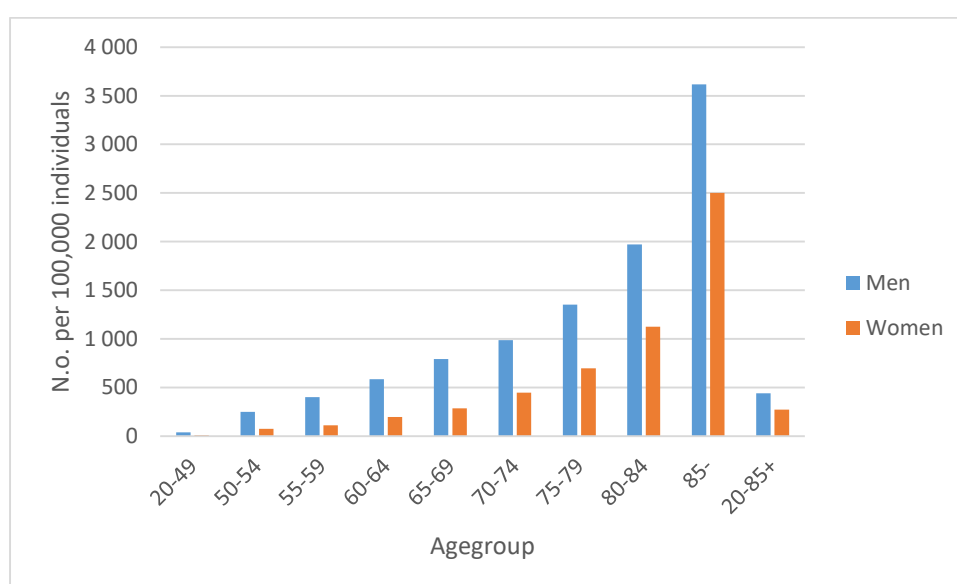


Figure 1: First incidence of myocardial infarction (after 7 years free of the disease) by sex and age group. Y axis shows number per 100,000 individuals residing in Sweden 2016. Source: National Board of Health and Welfare, <https://www.socialstyrelsen.se/statistik/statistikdatabas/hjartinfarkter>

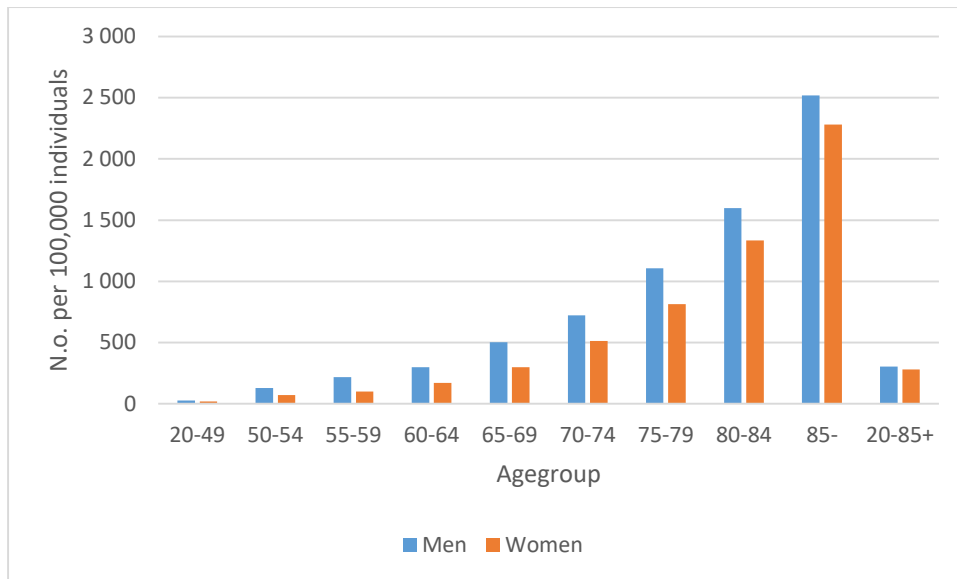


Figure 2: First incidence of stroke (after 7 years free of the disease) among Swedish inhabitants by sex and age group. Y axis shows number per 100,000 individuals residing in Sweden 2016. Source: National Board of Health and Welfare, <https://www.socialstyrelsen.se/statistik/statistikdatabas/stroke>

Among individuals who suffered a MI in Sweden in 2017, 17 % died the same day, 25 % died within 28 days, and 35 % died within a year. The corresponding proportions for stroke were 14 %, 25 % and 36 %. These proportions increase by age at the disease event, and are rather similar for women and men (National Board of Health and Welfare 2018b and 2018c).

In 2015, the number of men and women living with CVD in Sweden was 492,943 and 410,015, respectively (Wilkins et al. 2017), corresponding to a prevalence of about 13 % in men and 11 % in women aged 20 or older.

Among the cardiac arrhythmias, atrial fibrillation (AF) is the most common and its prevalence is increasing (Lau et al. 2017). In 2011, the AF prevalence among Swedish inhabitants above the age of 20 was 2.9 % (SBU 2013). AF may lead to stroke, heart failure or other heart related complications.

Heart failure is a condition – chronic or acute – in which the heart has a reduced ability to pump and/or fill with blood. The prevalence of chronic heart failure in most countries is about 1-2 % and steadily increases, most likely due to an ageing population and an improved survival in this patient group (Savarese and Lund 2017).

#### Established cardiovascular risk factors

In addition to male sex and increasing age, the non-modifiable cardiovascular risk factors include a family history of CVD, often defined as having at least one close relative who suffered a CVD event at an early age. A family history of CVD is considered a marker of genetic susceptibility, although the clustering of CVD events within families to a certain extent

may also reflect an aggregation of traditional cardiovascular risk factors in these families. The magnitude by which a family history of CVD modifies the future risk of CVD depends on the number and age of close relatives affected (Leander et al. 2001; Lloyd-Jones et al. 2004). Studies of twins have contributed with firm evidence that CVD has an important genetic component (Marenberg et al. 1994). Moreover, genome wide association (GWA) studies have during recent years identified a number of genetic variants associated with CVD and with morbidities closely related to CVD such as diabetes and obesity. However, the causal mechanisms behind CVD are complex and multiple genes seem to exert only weak effects. Clearly, environmental factors including lifestyle factors play a dominant role in CVD development. Further, it is generally thought that important gene-environment interactions remain to be identified.

Smoking, physical inactivity, an unhealthy diet (see Chapter 3) and a high alcohol consumption are all considered established modifiable cardiovascular risk factors (Stewart et al. 2017). The morbidities that constitute established CVD risk factors are diabetes, obesity, hypertension, and dyslipidemia (Stewart 2017; Wong 2014).

There is also clear evidence of an inverse association between socioeconomic position and several CVDs (de Mestral and Stringhini 2017; Kilpi et al. 2017). Recent Swedish data show associations between living in a low-socioeconomic status area and coronary artery calcification – a finding which possibly is explained by a high burden of cardiovascular risk factors in the socioeconomically deprived areas (Djekic et al. 2018). In 2015, the American Heart Association (AHA) published a scientific statement advocating a more pronounced “social determinants approach” in cardiovascular research to curb the burden of CVD morbidity and mortality (Havranek et al. 2015). The World Health Organization (WHO) defines “social determinants” as “the circumstances in which people are born, grow up, live, work and age, and the systems put in place to deal with illness” (WHO 2019). WHO further states: “These circumstances in turn are shaped by a wider set of forces: economics, social policies, and politics.” (WHO 2019). Recently, the AHA specifically addressed adverse cardiovascular effects associated with limited health literacy (the capacity to access and process basic health information needed to make appropriate health decisions) (Magnani et al. 2018).

Psychosocial stress has been much studied in relation to CVD, both concerning acute stress, such as acute emotional stressors and acute exposure to natural disasters, and concerning chronic stress, such as job stress, marital discord and bereavement. However, although some guidelines recommend stress management in individuals at high risk of CVD (Piepoli et al. 2016), psychosocial stress is not included in most current guidelines for primary CVD prevention (Dar et al. 2019).

### Cardiovascular disease aetiology

As discussed above, CVD is a complex disease, influenced by a combination of multiple genes and environmental factors. It is considered to develop through a large number of different mechanistic pathways, involving genetic as well as environmental influences. In Chapter 2 of this report, such mechanistic pathways are reviewed, with particular focus on the development and progression of atherosclerosis, the major underlying cause of CVD. Atherosclerosis is nowadays recognized as an inflammatory process in the artery wall, which may lead to

cardiovascular events such as MI or ischemic stroke when the atherosclerotic plaques become vulnerable and thrombogenic material comes in contact with the blood stream. A schematic drawing of CVD aetiology is shown in Figure 3. In cardiovascular research, CVD related morbidities such as hypertension and dyslipidemia are often studied as separate endpoints and generally considered “intermediate endpoints”. Given the multiple causal pathway leading to CVD, it is a challenge to identify its determinants.

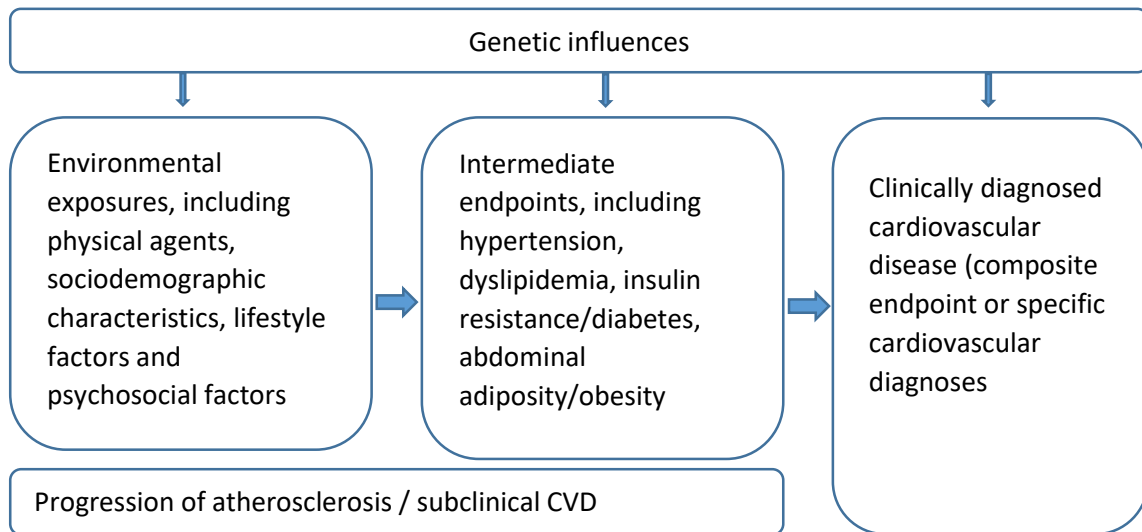


Figure 3. Schematic drawing of cardiovascular disease (CVD) aetiology, with examples of intermediate cardiovascular conditions.



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## 2. Environmental factors in atherosclerosis in relation to inflammation

Author: Johan Frostegård

### Introduction – atherosclerosis and CVD as chronic inflammatory conditions

Atherosclerosis including its complications is the major underlying cause of CVD. Many risk markers have been described, but real risk factors, also implying causation, are not so many: smoking, hypertension, diabetes and dyslipidemia. Most likely also chronic inflammation can now be added to this list (Benjamin et al. 2017; Timmis et al. 2018; Frostegård 2013a).

During recent years, it has become clear that atherosclerosis is an inflammatory disease process where the immune system plays an important role. In atherosclerosis, activated immune competent cells producing mainly pro-inflammatory cytokines are abundant. Dead cells and oxidized low density lipoprotein (OxLDL) represent other major constituents of the plaque (Frostegård et al. 1999).

The cause of the chronic inflammation and immune activation in atherosclerosis has not been fully defined, and there are different, non-mutually exclusive and potentially synergistic possibilities including OxLDL, heat shock proteins (HSP) and infections. Also systemic inflammation increases the risk of atherosclerosis, as in rheumatic diseases, especially systemic lupus erythematosus (SLE), but also other conditions like rheumatoid arthritis (RA) and it is possible that pro-inflammatory cytokines, if raised, could play a role in promoting also inflammation in atherosclerosis (Frostegård 2005).

Atherosclerosis in itself is in general not enough for development of CVD; rupture or erosion of atherosclerotic plaques is also a prerequisite. To identify factors that promote plaque rupture or erosion is thus one of the major challenges of today within CVD research (Frostegård 2013a).

Many experiments in animal models indicate that anti-inflammatory and immune modulatory treatment can ameliorate the progress of atherosclerosis. However, not until recently, anti-inflammatory treatment has been demonstrated to have significant and positive effects in humans.

This was demonstrated in the CANTOS study, where an inhibitor of Interleukin (IL)-1, (a monoclonal antibody), was reported to significantly decrease the risk of MI in individuals at risk, thus giving support to the inflammation hypothesis in atherosclerosis (and thus CVD) (Ridker et al. 2017).

In animal experiments and other experimental systems, immune modulation has been reported to ameliorate atherosclerosis. For example, active immunization can influence the degree of atherosclerosis in animal experiments; antigens used where atherosclerosis is ameliorated include OxLDL (or forms of modified low density lipoprotein (LDL) (Freigang et al. 1998; Palinski et al. 1995), phosphorylcholine (PC) (Caliguri et al. 2007) and where atherosclerosis instead is increased, heat shock protein 60 (HSP60) is an example (Frostegård 2013a; Xu et al. 1992).

The oxidation hypothesis in atherosclerosis, was originally proposed by D Steinberg and co-workers, as a general concept, with focus on LDL oxidation, since OxLDL is abundant in lesions (Steinberg et al. 1989). Early studies demonstrated that oxLDL can activate major immune competent cells in atherosclerosis, including B-cells, T-cells, monocytes/macrophages and endothelial cells; it was also shown that the phospholipid moiety, e.g. lysophosphatidylcholine (LysoPC), oxidized phospholipid 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphorylcholine (OxPAPC), lysophosphatidylcholines (LPC) and platelet activating factor (PAF)-like phospholipids with PC as the main epitope, in oxLDL causes pro-inflammatory effects and immune activation (including interferon (IFN)-gamma induction) (Frostegård 2013a; Frostegård et al. 1997a; Huang et al. 1999; Watson et al. 1997). Environmental factors which could promote LDL oxidation could therefore play a direct role in increasing inflammation and immune activation in atherosclerosis and CVD.

There are also defence mechanisms against oxLDL and its components. Antibodies against PC (anti-PC), especially IgM, were noted to be negatively associated with atherosclerosis development, risk of CVD in different contexts, and also with rheumatic conditions as RA and SLE (Sobel et al. 2013; Grönwall et al. 2012; Bashi et al. 2015; Gleissner et al. 2015; Wilde et al. 2015; Bashi et al. 2015; Imhof et al. 2015; Aprahamian et al. 2015). Interestingly, results point at differences in relation to sex and age which are not yet fully understood. At least five potential mechanisms which could explain the protective properties of anti-PC have been identified, and relate to that anti-PC is 1) anti-inflammatory (Su et al. 2008), 2) decreases the uptake of oxLDL in macrophages (de Faire et al. 2010), 3) inhibits cell death (Fiskesund et al. 2012) and 4) increases uptake of dead cells (McMahon and Skaggs 2016). A potential fifth mechanism is induction of T regulatory cells by anti-PC (Sun et al. 2017). Dysfunctional clearance of dead cells is likely to be important in driving inflammation in atherosclerosis, since cell material not cleared properly has inflammatory properties (Frostegård 2013b).

Dendritic cells (DCs) are specialized immune competent cells, which may play a major role in atherosclerosis, both at early stages and late, in relation to plaque complications and rupture. DC and T-cells co-localize in plaques, often in sites of plaque rupture, and their interaction could play an important role for immune activation in atherosclerosis (Frostegård 2013a). In an experimental system where T-cells from atherosclerotic plaques are exposed to DCs from the same individual, after being treated with different antigens, it was demonstrated that modified forms of LDL, including enzymatically modified and oxidized LDL, promote DC-induced T-cell activation (Frostegård et al. 2016; Liu et al. 2015). One antigen could be HSP60, which is induced by OxLDL, and in fact functions as a classical T-cell antigen in this context (Rahman et al. 2017). HSP60 is of interest because it is induced by stress, and this group of proteins is in fact often called stress proteins. Previous studies indicate that antibodies against HSP60 are risk markers, associated with CVD and atherosclerosis, and also hypertension, thus providing a link between immunity and this important risk factor (Wick et al. 1994; Xu et al. 1993; Pockley et al. 2000; Frostegård et al. 1997).

Yet another line of evidence may support the inflammatory concept in atherosclerosis, namely pleiotropic effects of statins, widely used as LDL cholesterol lowering drugs, especially after CVD, but also as primary prevention. By inhibition of prenylation, statins may exert an anti-inflammatory effect, by influencing cytokine production (Frostegård et al. 2016). Recently, proprotein convertase subtilisin kexin 9 (PCSK9) was demonstrated to target the LDL-receptor (LDLR), which results in increased LDL-levels. Inhibitors of PCSK9 were developed, and are

now in clinical use. Interestingly, findings suggest that PCSK9 (and its inhibition by silencing) could play a role in immune modulation in atherosclerosis irrespective of its lipid lowering capacity (Liu et al. 2018).

### The environment in atherosclerosis and CVD – general considerations

Environmental pollution plays an important role in CVD, and much focus has been on air pollutants and noise during recent years (see separate chapters in this report), but also on other factors like trace and heavy metals. There are many studies where positive associations between air pollution and CVD in general have been described (Munzel et al. 2017a). Environmental factors which influence inflammatory and immune reactions could contribute to atherosclerosis and thus CVD through different pathways, undoubtedly of which only some are well described. In general, ambient noise and air pollution are believed to be of major importance among environmental risk factors, but also other ones as heavy metals could be of importance (Munzel et al. 2017b).

While it has become clear that atherosclerosis is a chronic inflammatory condition, and CVD could thus also be described as such, the role of genes versus environment, and also their interplay is not clear in detail and appears to be very complex. Available findings indicate that the environment plays an important role. This comes from several lines of evidence, both epidemiological and experimental. Among the epidemiological studies, large ones suggest that adopting a healthy lifestyle, following recommendations by official organs such as the AHA, is associated with a huge reduction in risk of CVD; figures of 50 % reduction and more, even up to 80-90 % have been reported (Stampfer et al. 2000; Chiuve et al. 2008; Åkesson et al. 2007). One should still bear in mind that such studies cannot prove causation, due to their design, but are nevertheless hypothesis-generating and also supported by experimental evidence related to the different risk factors, such as hypertension, smoking, dyslipidemia and diabetes.

Clearly adding to this evidence and much in line with the topic herein are studies where changes in CVD risk are associated with changes in general environmental factors, not only established risk factors. Examples come from different countries in different types of development including China, Finland and United Kingdom (Bhatnagar 2017; Critchley et al. 2004; Pekka et al. 2002; Unal et al. 2004); changes in environment, e.g. concerning pollution, access to walkable areas, urban greenspace and better nutrition, within the same genetic context, were clearly associated with a significant change in risk – either increased or decreased risk depending on circumstances.

### Air pollution and inflammation in atherosclerosis

#### Associations with atherosclerosis and inflammation – epidemiological evidence

Among environmental factors described in atherosclerosis, air pollution is believed to be a major one (Munzel et al. 2017b). There could be several mechanisms involved, non-mutually exclusive, and in a recent review, three such mechanisms were high-lighted: "systemic spillover", autonomic imbalance, and circulating particulate matter constituents (Franklin et al.

2015). Air pollutants are emitted from a range of both man-made and natural sources. Details about air pollutants are described in Chapter 5. Observed associations between exposure to second-hand smoke and cardiovascular health outcomes add additional support to the increased risk of CVD associated with air pollution (Callinan et al. 2016). There is also room for other risk factors than the traditional ones (hypertension, dyslipidemia, diabetes and smoking), and sometimes figures of 10-25 % as a wiggle room for new risk factors are mentioned (Franklin et al. 2015). For example, hypertension could perhaps be influenced by immunological factors such as HSP60-immunity, since antibodies to HSP60 are associated with borderline hypertension and hypertension, and could promote atherosclerosis. As determined by animal experiments, hypertension could cause increased stress to the arterial wall, leading to increased expression of stress proteins, such as HSP60, and a proinflammatory immune reaction which could promote atherosclerosis. In human atherosclerosis, HSP60 causes a major histocompatibility complex (MHC)-class II and DC mediated pro-inflammatory T-cell activation (Xu et al. 1992; Rahman et al. 2017; Frostegård et al. 1997; Pockley et al. 2002). Cause and effect are difficult to discern, and atherosclerosis and hypertension could in principle promote each other.

In a recent large study, air pollution was linked to inflammatory and other factors of direct relevance for atherosclerosis, even though the design of the study does not allow for conclusions about causation. Both long term and short term concentrations of air pollution associated with different markers known to be related to atherosclerosis, namely markers of inflammation, coagulation and endothelial activation. There were significant, albeit relatively modest, associations with ambient fine particulate matter. Long term ambient fine particulate matter was associated with IL-6, an inflammatory marker, and short term ambient fine particulate matter with C-reactive protein (CRP), fibrinogen, and E-selectin (Hajat et al. 2015). CRP is known to be associated with atherosclerosis and CVD, though it is not clear if this indeed reflects causation, since CRP itself may have both positive and negative effects in this context. Fibrinogen and E-selectin are also likely to promote thrombosis in inflammation, which is an important aspect of atherosclerosis complications (Frostegård 2013).

The association between air pollution and atherosclerosis measures has been discussed and it should be noted that intima-media thickness (IMT) of the common carotid artery (CIMT), an often used measure and also marker of atherosclerosis, does not necessarily reflect the degree of inflammation in atherosclerosis. However, it could also be argued, that an increase of CIMT still has a basis in inflammation. In a recent and cross-sectional large meta-analysis including four European cohorts and taken together, 9,183 individuals, CIMT was determined, in association with air pollutants. Even though the meta-analysis indicated a positive association between CIMT and air pollutants, it did not reach significance and the non-significant estimated increase in CIMT was in fact not impressive: 0.72 % per  $5\mu\text{g}/\text{m}^3$  increase in particulate matter with diameter less than  $2.5\ \mu\text{m}$  ( $\text{PM}_{2.5}$ ) and 0.42 % per  $10^{-5}/\text{m}$  increase in  $\text{PM}_{2.5}$  absorbance. Further, proximity to high traffic was also positively but not significantly associated with CIMT (Perez et al. 2015). An extended meta-analysis with three other studies included did not in general change these findings (Perez et al. 2015). Passive smoking, as an environmental factor in atherosclerosis and CVD has been much discussed. A recent meta-study indicates that at least for PAD, there is a significant association (Ngu and McEvoy 2017).

### Mechanisms for air pollution and inflammation in atherosclerosis – experimental evidence

There are several recent reviews summarizing findings on and discussing air pollution and in vivo experimental evidence of a causative link. Air pollution of course represents a complex mixture from man-made and natural sources and includes gases, liquids and particles (Munzel et al. 2017b; Niemann et al. 2017). Direct in vivo evidence of a causative link between air pollution and inflammatory aspects of atherosclerosis, including foam cells (mostly macrophages, filled with lipid), comes from several studies. Below are two examples of the most interesting and relevant ones, which provide good evidence that associations reported between air pollution and CVD indeed reflect causation: 1) Humans were exposed short term to wood-smoke particles at relevant levels and markers of inflammation, coagulation and possible oxidative stress were raised, thus providing a possible mechanistic link to inflammation in atherosclerosis in humans (Barregård et al. 2006; Barregård et al. 2008), and 2) An impairment of endothelial function was reported, in humans, after exposure to diesel, which occurred together with mild systemic inflammation with increased levels of important pro-inflammatory cytokines – tumor necrosis factor (TNF)-alpha and IL-6 – and a lasting effect for at least 24 h after exposure (Törnqvist et al. 2007). These cytokines are actively produced in the plaque and are likely to play an important role in promoting inflammation in atherosclerosis (Frostegård et al. 1999).

Even though it does not provide a direct link to plaque T-cells, it is still interesting to note that air pollution potentiates a pro-inflammatory T helper cell 1 (Th1) response both in lungs and systemically, in a mouse model (Deiuliis et al. 2012).

In one study from 2005, the hypothesis that exposure to environmentally relevant particulate matter in air pollution would accelerate atherosclerosis was tested in apoE knock out (k/o) mice which were fed either normal chow or high fat chow. The animals were exposed to concentrated ambient PM<sub>2.5</sub> or filtered air for 6 h per day, 5 days per week for a total of 6 months. Composite atherosclerotic plaque was increased as compared to controls in both diet groups, and reached significance in the high fat group (which mimicks human atherosclerosis better) and in this group there was also increased inflammation in plaques, as determined by macrophage content. Further, endothelial function was better in control groups. Thus, in this apoE k/o mouse model, long-term exposure to low concentration of PM<sub>2.5</sub> altered vasomotor tone, induced vascular inflammation, and increased atherosclerosis (Sun et al. 2005). In another important study much of this data was confirmed, and also extended in atherosclerosis-prone ApoE<sup>-/-</sup> or LDLR<sup>-/-</sup> mice which were exposed to filtered air or concentrated ambient PM<sub>2.5</sub> for 6 months. Interestingly, macrophages in exposed animals had an increased oxLDL-uptake capacity, and atherosclerosis measures increased, including foam cell formation. Oxidized lipids played a role in this (Rao et al. 2014). In yet another study, diesel exhaust was studied in apo E k/o mice fed regular chow. They were exposed to diesel exhaust for 7 weeks. Alveolar macrophages were 8-fold higher after this and plaque cellularity, foam cell formation and oxidative stress markers were also significantly increased, in a dose dependent manner (Bai et al. 2011).

In yet another study, a classical animal model was used, namely New Zealand White rabbits fed a high fat diet. They were exposed to ambient air PM<sub>10</sub> (particles less than 10µm) after balloon injury to abdominal aorta. The study reports that PM<sub>10</sub> exposure accelerated balloon catheter induced plaque formation and also increased intimal macrophages and lipid

accumulation. Another finding is that PM<sub>10</sub> impaired vascular acetylcholine (ACh) responses and raised vasoconstriction induced by phenylephrine, suggesting a potential role also in hypertension. Statins (Lovastatin) did not reduce lipids in the rabbit model, but still had a protective effect, decreasing atherosclerosis and improving endothelial function, which may be attributed to statins' anti-inflammatory properties (Miyata et al. 2013).

Oxidative stress has been much discussed as an underlying factor in many disease conditions, not least chronic inflammatory ones as CVD (and atherosclerosis) and there are many indications that air pollutants can be directly involved in causing oxidative stress and induction of free radicals which could in its turn cause or increase inflammation and immune activation in arteries and atherosclerotic plaques (Niemann et al. 2017). There are several relevant products of oxidative stress which could play a role in promoting LDL-oxidation, and malondialdehyde (MDA) is one example, since MDA is a major epitope in OxLDL (Frostedgård 2013a). Another example is OxPAPC, which has PC as a major pro-inflammatory epitope. It seems as if anti-PC and antibodies to MDA (anti-MDA) have protective properties, being anti-inflammatory, in the context of oxidative stress (Frostedgård 2013a; Thiagarajan et al. 2016; Rahman et al. 2016).

## Noise

Another factor where there is relatively much epidemiological evidence, supporting a potential role as risk factor in CVD, atherosclerosis and inflammation, in addition to air pollutants, is environmental noise, including traffic noise. This has been demonstrated to be associated with increased risk of CVD including MI, heart failure and stroke and also established risk factors as hypertension, blood lipids and coagulation factors (Munzel et al. 2018; Kempen et al. 2018; Fuks et al. 2017). These associations are confirmed in a recent large-scale meta-analysis (Vienneau et al. 2015). Recently, also the development of obesity was linked to exposure to transportation noise (Pyko et al. 2017). Of note, noise and air pollution may interact and even strengthen adverse effects (Pyko et al. 2017).

Noise has also been associated with psychological problems, including sleep disorders, stress and stress hormones (Munzel et al. 2016; Schmidt et al. 2013), depression and anxiety (Beutel et al. 2016) which by themselves have been associated with CVD and this is the case especially with chronic stress (Yusuf et al. 2004). Sleep disorders and sleep deprivation are well known for their numerous negative effects, which thus also include increased risk of CVD. Here mechanisms appear to be relatively well understood, since such disturbances are directly associated with increased pro-inflammatory inflammatory burden, with cytokines as IFN-gamma and IL-6 (Tobaldini et al. 2013; Nowakowski et al. 2018) which most likely are actively produced by immune competent cells in atherosclerotic plaques which are damaged or ruptured (Frostedgård 2013b).

Direct mechanisms which link noise with the vascular wall, atherosclerosis and its complications based on experimental studies where noise is implemented in an experimental setting involving both mice and men, have also been reported and are of interest. These include induction of endothelial dysfunction, increased oxidative stress and also procoagulant and proinflammatory effects, and increased blood pressure (Schmidt et al. 2015; Charakida and Deanfield 2013; Jarup et al. 2008; Munzel et al. 2017c; Turner et al. 2005). Also direct effects



on vascular structure, compatible with early stages of damage which could promote atherosclerosis were noted in mouse models, where also type of stress was of importance. Here aircraft noise in contrast to continuous white noise had a significant effect (Munzel et al. 2017c).

Underlying mechanisms could be indirect. Environmental noise is well known to be associated with and also cause sleep disorders, and other adverse emotional and cognitive responses which could result in chronic stress which could in its turn lead to chronic inflammation (Babisch 2003). Chapter 9 in the present report provides a comprehensive review of noise in relation to cardiovascular effects.

## Diet

The role of diet in CVD, atherosclerosis and related inflammation has been very much discussed and studied. The focus here is on inflammation in atherosclerosis whereas statistical and epidemiological associations with CVD are addressed in Chapter 3.

Studies of diet causing various degrees of inflammation in atherosclerosis are scarce, one reason is likely to be that such studies are difficult to perform in double-blinded randomized way, and in animal studies, one problem is that commonly used mice models are heavily genetically modified, since mice (and rats) do not develop atherosclerosis otherwise. There has been a tradition of large-scale epidemiological and registry studies, and more studies investigating underlying mechanisms leading to inflammation are needed. This discussion is ongoing, and thus, the role of diet in promoting inflammation in the artery wall is not so clear.

In a recent review of prospective cohort studies, systematic reviews and meta-analyses published in the period from 2014 to 2017 on the effects of saturated fatty acids (SFA) and *trans* fatty acids, where saturated fat, and also *trans*-fat replacement were studied, the results are striking and also disappointing for those who want clear cut evidence of the role of these fats in CVD and atherosclerosis. The authors report that “Results of the new large prospective cohort studies pertaining to the effect of SFA consumption on CVD risk are contradictory” (Makarewicz et al. 2018). However, there is a relatively broad consensus about variants of a Mediterranean diet as being beneficial. There is also an extensive literature where different kinds of anti-inflammatory diets are discussed and promoted, but this is not within the scope herein since the scientific basis is not so clear as discussed above.

Another novel field is studies of the microbiome in relation to different diseases. This field is emerging, and it appears too early to assess the impact on inflammation in atherosclerosis, and many studies are still mostly hypothesis-generating.

## Radiation

In cancer treatment, increased risk of CVD and atherosclerosis has been described, though this is more of a side effect than a classic environmental factor. Mechanisms may include endothelial damage, chronic inflammation, DNA-damage and increased oxidation (Min and Wierzbicki 2017; Sylvester et al. 2018). Other types of radiation, including space radiation,

may be implicated in atherosclerosis and inflammation, though the current knowledge appears to be limited (Sylvester et al. 2018).

### Season and circadian rhythms

Throughout human evolution, our bodies have been adapted to changes during the day and night, and there are well-known hormonal and other changes, for example, cortisol is at its lowest in before dawn, when also CVD, especially MI is more common (Muller et al. 1985; Cohen et al. 1997). This could shed light on the role of cortisol in CVD and inflammation, but much of this remains speculative. For example, could a low cortisol level promote inflammation (cortisol being potentially anti-inflammatory)? Could vulnerable individuals with inflamed and perhaps fissured plaques reach a tipping point when cortisol is low?

Chronic stress is well-known to be associated with CVD, and cortisol may have long term effects which could be detrimental, thus different from potential short term effects. Sleep disorders and raised cortisol promote obesity, hypertension and oxidative stress and are also associated with CVD and atherosclerosis (Martocchia et al. 2016).

Likewise, there is a variation in risk during the year, since CVD is more common in the winter. The underlying cause has been much debated, but most likely includes both increased risk of dyslipidemia, hypertension and potentially immunological changes, which could be associated with infections which are common in the winter. Also other negative factors could be present, such as low mobility (Marti-Soler et al. 2014).

### Heavy metals, organic pollutants, trace elements and others

#### Heavy metals

Environmental factors which could play a role in chronic inflammation and atherosclerosis are metals, including trace and heavy metals. Here, knowledge is relatively scarce. Systematic reviews indicate that among environmental metals, lead and cadmium are associated with atherosclerotic disease (Solenkova et al. 2014; Kamas et al. 2016). A mechanistic causative role is supported by evidence from animal models, where lead and cadmium accelerate atherosclerosis (Revis et al. 1981; Messner and Bernhard 2010).

In one interesting study, eleven heavy metals and trace elements were analysed in blood, using mass spectrometry and compared with determinations of atherosclerotic IMT and prevalence of plaques (by ultrasound) of coronary arteries. The study was cross-sectional, and included 1016 subjects, aged 70. Here, the associations between metals and IMT measures were modest and only significant for nickel, aluminium and chromium and the study did not focus on inflammation (Lind et al. 2012).

In a meta-analysis from 2016, essential environmental metals antimony, barium, chromium, nickel, tungsten, uranium, and vanadium were studied specifically, and it was concluded that evidence was too scarce to draw conclusions about these as risk factors for CVD (Nigra et al. 2016). Iron is another metal which has been much discussed but where there still appears to be low evidence of an association with atherosclerotic disease (Kraml 2017). In a recent

systematic meta-review, in addition to lead and cadmium, also copper was demonstrated to be associated with CVD, in contrast to other metals such as mercury (Chowdhury et al. 2018).

In addition to experimental evidence, also plausible molecular causes have been described. An obvious such is that metals can produce reactive radicals and induce oxidative stress (Jomova et al. 2011; Valko et al. 2005). Tightly connected with this is LDL-oxidation, and as we have seen, OxLDL is likely to be a major factor in inflammation in atherosclerosis. Indeed, in experiments showing that OxLDL induces differentiation and activation of monocytes/macrophages, and also activation of T-cells, LDL was oxidized by copper (Frostegård et al. 1990 and 1992). Metals may also directly damage the endothelium (Prozialeck et al. 2008).

### Arsenic

Another compound which is not clearly defined as a metal, is arsenic, which is well known to be associated with CVD, as recently reported in systematic meta-reviews, in one also in relation to atherosclerosis measures (Chowdhury et al. 2018; Kuo et al. 2017).

Animal experiments clearly demonstrate that arsenic causes increased atherosclerosis and inflammation. Mechanisms suggested include increased oxidative stress and activation of inflammatory cells (Srivastava et al. 2009; Makhani et al. 2018). Another direct mechanism is increased uptake of OxLDL in macrophages, thus forming inert foam cells which are typical of plaques (Hossain et al. 2013). This is supported by animal experiments, in which lipid load in plaque macrophages was increased (Makhani et al. 2018). A direct effect on endothelium by arsenic-related compounds has also been reported (Xu et al. 2017).

### Organic pollutants

Organic pollutants including various compounds as bisphenol A, phthalates, pesticides, and dioxin have been much discussed, but the evidence in relation to increased risk of CVD and atherosclerosis or inflammation in atherosclerosis is relatively scarce. A review from 2011 concluded that even though there are some such associations, the overall picture is not so clear (Lind and Lind 2012). In another study from 2015, reporting on effects of exposure to dioxin on mortality and morbidity, the associations were not strong though they did reach statistical significance in a subgroup studied (Collins et al. 2016). Still the knowledge about underlying mechanisms for such associations is relatively scarce. Interestingly, however, elegant experiments using a mouse model of atherosclerosis support a direct effect of dioxin through activation of inflammatory genes and also a macrophage-related effect (Wu et al. 2011).

### Conclusions and needs for research

Taken together, several lines of evidence indicate a link, also causative, between environmental factors and inflammation in atherosclerosis. Especially air pollution as one such cause, is supported by evidence, but also noise and some metals are well documented. However, further investigations of how exposure to environmental factors may promote inflammation in the artery wall are needed.

One area where more research is important is how climate factors could influence CVD. There could be both novel environmental factors, such as pollutants, and also infectious disease panorama changes. Also, it is important with studies on how dietary changes, with less meat and animal protein, affect CVD. In this context, both epidemiological and experimental animal studies should be included. This knowledge is a good basis for improved prevention and potentially also treatment of atherosclerosis and related chronic inflammation.

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### 3. Diet and dietary supplements

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#### Introduction

Diet may affect the risk of CVD via several pathways, for example through impacts on blood pressure, blood lipids, coagulation and thrombosis, oxidative stress, endothelial function, systemic inflammation, calcification, glucose and insulin concentrations and body weight. This part of the report summarizes current evidence from observational epidemiological studies, randomized controlled trials (RCT), and Mendelian randomization studies of the associations of dietary patterns, foods and beverages, selected nutrients and dietary supplement with risk of CVD. RCTs generally represent the most robust study design to establish causality, but dietary interventions, especially long-term primary interventions are complicated to perform and suffer from limitations such as lack of blinding, crossover, and noncompliance. Well-designed prospective studies, with complementary strengths and limitations have to serve as the basis for the implementation of prevention strategies. Nevertheless, Mendelian randomization studies, based on the fact that genetic polymorphisms are randomly distributed and unlikely associated with potential confounders, provide an alternative that is comparable to the strength of the RCT design.

#### Dietary patterns

RCTs have shown that adherence to healthy dietary patterns, including the Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets, results in significant decreases in blood pressure, total cholesterol concentrations, fasting glucose concentrations, and systemic inflammation (Soltani et al. 2018; Siervo et al. 2015; Domenech et al. 2014; Appel et al. 1997; Estruch et al. 2018). The features of the traditional Mediterranean diet are the use of olive oil as the main fat; high amounts of fruits, vegetables, nuts, legumes, cereals and grains (mainly whole grains); moderate amounts of fish and poultry; low amounts of dairy products, meat, and sweets; and moderate consumption of wine together with meals (Estruch et al. 2018). Such a diet is rich in fiber, vitamins, minerals, phenolic compounds, and unsaturated fatty acids, and low in sodium and saturated and *trans* fatty acids. An *a priori* score to estimate the adherence to a Mediterranean diet was developed by Trichopoulou et al. (2003) and is now commonly used along with various modified versions to estimate adherence to the Mediterranean diet in non-Mediterranean countries.

The PREvención con DIeta MEDiterránea (PREDIMED) trial was the first large RCT to evaluate whether primary CVD events could be reduced by adherence to a Mediterranean diet (Estruch et al. 2018). In the PREDIMED trial, 7,447 Spanish adults at high risk of CVD were randomly assigned to one of three diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts (walnuts, almonds and hazelnuts) or a control diet (advice on a low-fat diet) (Estruch et al. 2018). Compared with the control group (109 events), the hazard ratio (HR), adjusted for baseline characteristics and propensity score, of the primary endpoint of major CVD events (MI, stroke, or death from CVD) was 0.69 (95 % CI 0.53–0.91) for a Mediterranean diet with nuts (83 events) and 0.72 (95 % CI 0.54–

0.95) for a Mediterranean diet with extra-virgin olive oil (96 events) (Estruch et al. 2018). The Mediterranean diet with extra-virgin olive oil was further associated with a lower risk of AF (HR 0.62; 95 % CI 0.45–0.85) (Martinez-Gonzalez et al. 2014a) and with a non-significant lower risk of heart failure (HR 0.68; 95 % CI 0.41–1.13) (Papadaki et al. 2017). Observational prospective studies are consistent with an inverse association between a Mediterranean-like dietary pattern and risk of total CVD, coronary heart disease (CHD), stroke, and heart failure (Table 2) (Rosato et al. 2017; Tektonidis et al. 2015 and 2016).

The DASH diet is rich in fruits, vegetables, and low-fat dairy products and reduced in saturated and total fat (Appel et al. 1997). This diet has been shown to substantially reduce blood pressure in an RCT (Sacks et al. 2001). Data from observational prospective studies on the DASH diet in relation to risk of CVD are limited but available evidence indicates that high adherence to the DASH diet is associated with reduced risk of CHD, stroke, and heart failure (Table 2) (Larsson et al. 2016a; Kontogianni and Panagiotakos 2014; Salehi-Abargouei et al. 2013).

A healthy dietary pattern together with a low-risk lifestyle practice is likely to confer considerable protection against CVD. Such low risk behavior is, with the exception of eating a healthy diet and consuming moderate amounts of alcohol, characterized by a combination of behaviors such as refrain from smoking, being physically active, and avoiding obesity. RCTs testing a combined low-risk behavior in a long-term primary intervention are complicated and likely not feasible due to the reasons mentioned above. Thus, based on prospective studies alone, a low-risk diet and lifestyle is associated with between 40–80 % lower risk of MI, stroke, and heart failure as compared with a high-risk group with no low-risk behaviour (Larsson et al. 2014a, 2015a and 2016b; Åkesson et al. 2007 and 2014; Rutten-Jacobs et al. 2018). Similar results have been observed in groups at higher CVD risk due to diagnosis of hypertension or high cholesterol levels, or with a genetic risk score indicating an overall higher risk of CVD (Larsson et al. 2015a; Åkesson et al. 2014; Rutten-Jacobs et al. 2018; Khara et al. 2016). This may indicate that the majority of CHD events are likely to be avoided by primordial prevention which inhibits the initiation and establishment of any high-risk behavior.

### Fruit and vegetables

An inverse association of fruit and vegetable consumption with risk of any CVD, CHD, and stroke, but not heart failure, has been observed in most observational prospective studies (Table 2) (Bechthold et al. 2017; Aune et al. 2017). In a meta-analysis of 13 prospective studies, the summary relative risk (RR) of CVD per 200 g/day increment in fruit and vegetable consumption was 0.92 (95 % confidence interval [CI], 0.90–0.95) (Aune et al. 2017). Similar associations were observed for fruit and vegetables separately (Aune et al. 2017). Consumption of fruit (Stackelberg et al. 2013) and fruit and vegetables (Nordkvist et al. 2018) has also been reported to be inversely associated with risk of abdominal aortic aneurysm. Fruit and vegetables are rich sources of dietary fiber, micronutrients (e.g. vitamin C, folate, magnesium, and potassium), carotenoids, and phenolic compounds, which may lower the risk of CVD by reducing blood pressure (Appel et al. 1997) and improving endothelial function and through anti-oxidative, anti-inflammatory, and antithrombotic effects (Chen et al. 2013; Tang et al. 2016; Li and Xu 2014). Genetically higher serum magnesium concentrations have been observed to be associated with reduced risk of CHD (Larsson et al. 2018a) and ischemic stroke, particularly cardioembolic stroke (Larsson et al. 2019).

## Potatoes

Potatoes are abundant in starch (long chains of glucose), which is rapidly digested and often results in high glycemic response. Observational studies on potato consumption in relation to risk of CVD are limited but available data indicate that potato consumption does not affect the risk of CVD (Aune et al. 2017; Larsson and Wolk 2016).

## Grains

Meta-analyses of observational studies have shown that high consumption of whole grains, which are important sources of fiber, B vitamins, and certain trace minerals (e.g. magnesium, zinc, and iron), is associated with reduced risk of CHD and heart failure but not stroke (Table 2) (Bechthold et al. 2017; Aune et al. 2016a). Refined grain consumption appears neutral for CVD risk (Bechthold et al. 2017; Wu et al. 2015).

## Olive oil and monounsaturated fat

Studies on olive oil consumption in relation to risk of CVD are limited. A meta-analysis of prospective studies showed that a 25 g/day increase in olive oil consumption was associated with a reduced risk of stroke (RR 0.74; 95 % CI 0.60–0.92; n=2 studies) but not CHD (RR 0.96; 95 % CI 0.78–1.18; n=4 studies) (Martinez-Gonzalez et al. 2014b). In the PREDIMED trial, the RR of the primary endpoint of major CVD events (MI, stroke or CVD death) was 0.72 (95 % CI, 0.54–0.95) for a Mediterranean diet supplemented with extra-virgin olive oil compared with the control group advised on a low-fat diet (Estruch et al. 2018). Olive oil is rich in monounsaturated fatty acids (primarily oleic acid), which are not significantly associated with CVD (Schwingshackl et al. 2014).

## Nuts and legumes

Overall results from meta-analyses of prospective studies have shown that nut consumption is significantly inversely associated with mortality from CVD and CHD but not with risk of stroke or heart failure (Table 2) (Bechthold et al. 2017; Aune et al. 2016b). The RR of CVD mortality per 28 g/day increase in nut intake was 0.79 (95 % CI 0.70–0.88; n=12 studies) (Aune et al. 2016b). In a recent prospective study of 61,364 Swedish adults, nut consumption was inversely associated with incidence of non-fatal MI, heart failure, AF, and abdominal aortic aneurysm after adjustment for age and sex only (Larsson et al. 2018b). However, adjustment for multiple risk factors attenuated these associations and only a linear, dose-response association with incident AF remained (RR for  $\geq 3$  times/week versus no consumption, 0.82; 95 % CI 0.68–0.99) (Larsson et al. 2018b). Nut consumption was not associated with risk of aortic valve stenosis or stroke (Larsson et al. 2018b). The average nut consumption in Sweden is low (5 g/day) (Eneroth et al. 2017) and lack of a sufficient exposure gradient, together with a likely scenario of salt being consumed together with the nuts/peanuts, may explain the absence of any clear protective association with CHD incidence in the Swedish cohorts. In the PREDIMED

trial, the RR of the primary endpoint of major CVD events (MI, stroke, or CVD death) was 0.69 (95 % CI, 0.53–0.91) for a Mediterranean diet supplemented with nuts (Estruch et al. 2018). Based on a scenario where the results from the nut intervention group in the PREDIMED trial was applied to the Swedish population, the number of CVD events potentially avoided given a consumption of a handful nuts per day was over 7,000 in one year (Eneroth et al. 2017). Legume consumption appears neutral for stroke risk (Bechthold et al. 2017; Afshin et al. 2014), but is inversely associated with CHD risk (Bechthold et al. 2017).

### Chocolate

Meta-analyses of prospective studies have shown that chocolate consumption is significantly inversely associated with risk of CHD (Larsson et al. 2016c) and stroke (Table 2) (Larsson et al. 2012a), but is not associated with risk of AF (Larsson et al. 2018c). Low-to-moderate but not high chocolate consumption has been found to be associated with lower risk of heart failure (Table 2) (Gong et al. 2017). Cocoa and chocolate are rich in flavanols, which may reduce the risk of CVD by improving endothelial function and reducing blood pressure, oxidative stress, platelet aggregation, and insulin resistance (Larsson 2014).

### Dairy products and calcium

Dairy product consumption appears neutral for risk of CHD, stroke, and heart failure (Table 2) (Bechthold et al. 2017; de Goede et al. 2016; Larsson et al. 2012b), though inverse associations of milk and low-fat dairy consumption with stroke risk were observed in Asian studies (de Goede et al. 2016) and Swedish cohorts (Larsson et al. 2012b), respectively. For the specific dairy products, cheese consumption has been inversely associated with CHD in Swedish cohort studies (Patterson et al. 2013; Sonestedt et al. 2011), indicating that dairy foods is a heterogeneous group with respect to CVD health. Dairy products are rich sources of calcium. High serum calcium concentration, e.g. due to calcium supplementation or genetic predisposition, has been demonstrated to be positively associated with risk of CVD, CHD, and stroke (Chowdhury et al. 2012; Rohrmann et al. 2016; Bolland et al. 2011; Larsson et al. 2017a). Results from a meta-analysis of RCTs showed that calcium supplementation was associated with an increased risk of MI (RR 1.24; 95 % CI 1.07-1.45; n=7 trials) (Bolland et al. 2011). Genetic predisposition to higher serum calcium concentrations has been shown to be associated with an increased risk of CHD (Larsson et al. 2017a), but not ischemic stroke (Larsson et al. 2019). High serum calcium concentrations may increase the risk of CHD by increasing carotid artery plaque thickness and aortic calcifications (Bolland et al. 2011), and possibly through effects on heart rhythm.

### Fish, omega-3 fatty acids, and vitamin D

Observational studies suggest that fish consumption is associated with a modest reduced risk of CHD, stroke, and heart failure (Table 2) (Bechthold et al. 2017; Larsson and Orsini 2011a), but is not associated with AF (Larsson and Wolk 2017). Biomarker levels of fish-derived omega-3 fatty acids have been found to be associated with a modestly lower incidence of fatal

CHD (Del Gobbo et al. 2016). However, a recent meta-analysis of 10 RCTs showed no significant association of fish-derived omega-3 fatty acids supplements with risk of fatal or non-fatal CHD or any major vascular events (Aung et al. 2018), (see paragraph on Dietary supplements below for more information).

Fatty fish is a good source of vitamin D, which has been found to be inversely associated with risk of CVD in observational studies (Chowdhury et al. 2012; Zhou et al, 2018; Zhang et al. 2017). However, the association is likely explained by confounding or reverse causality. Mendelian randomization studies, which are less prone to bias compared with observational studies, have shown no association between genetically higher circulating 25-hydroxyvitamin D concentrations and risk of coronary artery disease (Manousaki et al. 2016) or ischemic stroke (Larsson et al. 2018d). Moreover, in a large randomized controlled trial, supplementation with vitamin D for five years did not result in a lower incidence of cardiovascular events (see paragraph Dietary supplements below) (Manson et al. 2019a). Fish may also contain dietary contaminants, such as methyl mercury, organochlorines, and perfluorinated compounds. Exposure to these contaminants may mask the beneficial effect of fish on CVD health (see Chapter 4).

## Eggs

Eggs are good sources of protein and micronutrients but are also high in cholesterol and may increase serum cholesterol concentrations. Meta-analyses of prospective studies conducted mainly in European and US populations have found no evidence that consumption of up to 1 egg per day increases the risk of CHD or stroke, but suggested a positive association with heart failure (Table 2) (Bechthold et al. 2017; Rong et al. 2013; Larsson et al. 2015b). In contrast, recent results from a cohort study of over 0.5 million Chinese adults showed that daily egg consumption was associated with a significant 11 % lower risk of CVD compared with never or very rare consumption of eggs (Qin et al. 2018). The Chinese study also found that daily egg consumption was associated with reduced risk of CHD (RR 0.88; 95 % CI 0.84–0.93), haemorrhagic stroke (RR 0.74; 95 % 0.67–0.82), and ischemic stroke (RR 0.90; 95 % 0.85–0.95) (Qin et al. 2018).

## Meat and sodium/salt

The overall evidence from prospective studies indicates that high consumption of red meat, in particular processed meat (i.e. sodium- and nitrite-preserved meats such as bacon, ham and sausages), is associated with an increased risk of CVD (Table 2) (Bechthold et al. 2017; Kaluza et al. 2012). Processed meats contain added sodium, which raises blood pressure in a dose-dependent fashion (Aburto et al. 2013; Sacks et al. 2001) and is positively associated with risk of stroke and fatal CHD (Aburto et al. 2013). A systematic review and meta-analysis of 185 RCTs showed that sodium reduction results in a significant decrease in blood pressure, in particular in individuals with hypertension (Graudal et al. 2017).



### Sugar-sweetened beverages

Prospective studies of sugar-sweetened beverage consumption in relation to risk of CVD are relatively limited. The overall evidence indicates that sugar-sweetened beverage consumption is positively associated with risk of CHD, stroke, and heart failure (Bechthold et al. 2017; Rahman et al. 2015; Larsson et al. 2014b). High consumption of sugar-sweetened beverages may increase the risk of CVD by raising blood glucose concentrations, which appear to be a risk factor for CVD (Bragg et al. 2016; Benn et al. 2012), or by increasing body weight.

### Coffee and tea

Prospective studies have reported that moderate coffee consumption is associated with a 10–30 % reduced risk of CVD mortality (Crippa et al. 2014; Ding et al. 2014; Gunter et al. 2017), fatal and non-fatal CHD (Ding et al. 2014; Park et al. 2017), stroke (Ding et al. 2014; Park et al. 2017; Larsson and Orsini 2011b), and heart failure (Mostofsky et al. 2012). Coffee consumption seems neutral for AF (Larsson et al. 2015c). Tea consumption has also been observed to be inversely associated with risk of CHD and stroke (Zhang et al. 2015). Coffee and tea are major sources of caffeine and are rich in phenolic compounds (e.g. chlorogenic acids), which modestly lower blood pressure and could possibly decrease lipid peroxidation and improve endothelial function (Larsson 2014).

### Alcohol

Results from meta-analyses of prospective studies have shown that light or moderate alcohol drinking is associated with reduced risk of CHD (Larsson et al. 2017b; Ronksley et al. 2011), ischemic stroke (Larsson et al. 2016d), and heart failure (Larsson et al. 2017c) (Table 2), but the causality of these associations is uncertain. Limited data also suggest that light alcohol consumption is associated with reduced risk of aortic valve stenosis (Larsson et al. 2017d) and abdominal aortic aneurysm (Stackelberg et al. 2014). In contrast, alcohol consumption increases the risk of AF in a dose-response manner (Larsson et al. 2014c), and high or heavy alcohol drinking increases the risk of ischemic and haemorrhagic stroke (Larsson et al. 2016d) as well as cardiomyopathy, liver disease, some cancers, accidents and violence. Alcohol consumption is therefore not recommended as a means to possibly reduce the risk of some CVD outcomes.

### Food additives and food processing

Less is known about the potential effect of food additives and food processing on CVD risk. More recently, the added phosphorous (e.g. phosphate) – a preservative that also brings flavor, texture and taste to processed food, and absorbed to 100 % in the gastrointestinal tract – increases phosphate in plasma to a much higher extent than naturally occurring phosphate (Moore et al. 2015). High-to-normal plasma phosphate concentration, as well as increased intake of phosphate, have been associated with increased risk of CVD and accelerated ageing in the general population (Chang et al. 2014; Dhingra et al. 2007; McClelland et al. 2016). The main pathophysiological effect of phosphate is vascular damage, e.g. endothelial dysfunction,



and vascular calcification. There is a plentiful exposure to phosphate additive via a large variety of processed food, whether its potential negative impact on CVD health is underappreciated needs to be verified.

It has been proposed that the increased supply of highly processed foods is a central contributor to the obesity epidemic (Swinburn et al. 2011), a major underlying risk factor for CVD, with the most important theoretical links related to their motivational (i.e. rewarding) potential. Precisely engineered to be highly palatable by careful manipulation of flavor, texture and content of sugar, fat and salt, ultra-processed foods provide pleasure via a strong reinforcement value that can promote excess energy intake by overriding the homeostatic mechanism regulating food intake (Berthoud et al. 2006). The reinforcement process is mainly mediated by the mesolimbic dopamine system and involves dopamine release in the ventral striatum (Kenny 2011). Ultra-processed foods are often cheap, highly marketed, and ready to consume and almost always available for consumption, creating an effort-reward balance further favoring consumption of processed foods.

### Dietary supplements

Dietary supplements, e.g. vitamins and minerals in concentrated form, are regulated as foods in Sweden. Supplements are sold in concentrated form of capsules, tablets, powders, ampoules of liquid or drip bottles with the purpose of complementing the usual diet. During 2016, various types of dietary supplements were sold for a sum of almost 5 billion SEK in Sweden. The prevalence of supplement use varies between 20–50 % depending on age, sex, education and country. The main reasons provided for using dietary supplement is either to improve or maintain health (Rautiainen et al. 2016). Although the dietary habits in the population are considered suboptimal with too low consumption of fruit vegetables, whole meal products and fish and too high consumption of salt and sugar, representative dietary surveys show that most people get enough vitamins and minerals through their food.

Based on large systematic reviews of RCTs it is concluded that individual high doses of  $\beta$ -carotene and vitamin E are not recommended, and may on the contrary be harmful (Fortmann et al. 2013; U.S Preventive Service Task Force 2016). Similar findings were recently observed for niacin and antioxidant mixtures (Jenkins et al. 2018). In general, the data on multivitamins and on single- or paired-nutrient supplements show no consistent benefit for the prevention of CVD, MI, or stroke. Thus, the current evidence is insufficient to assess the balance of benefits and harms and the conclusive evidence for the benefit of any supplement across all dietary backgrounds (including deficiency and sufficiency) has not been demonstrated (Jenkins et al. 2018). Just recently the up-to-date largest randomized trial was published (Manson et al. 2018a and 2018b). A nationwide, 5-year placebo-controlled trial, with a two-by-two factorial design, of vitamin D3 (2000 IU/day) and marine omega-3 fatty acids (1 g/day) for the prevention of CVD (and cancer) among >25,000 women and men in the US. The vitamin D dose group, corresponding to about 5 times the recommended daily intake of vitamin D, experienced 396 primary CVD events (a composite of MI, stroke, or CVD death), while 409 events occurred in the placebo group; RR 0.97; 95 % CI 0.85–1.12;  $p=0.69$ ). In the analyses of secondary end points, the RRs were as follows: for the expanded composite end point of major CVD events plus coronary revascularization, 0.96 (95 % CI 0.86–1.08); for MI, 0.96 (95 % CI 0.78–1.19); for stroke, 0.95 (95 % CI 0.76–1.20); and for death from CVD causes, 1.11 (95 % CI 0.88–

1.40). No excess risks of hypercalcemia or other adverse events were identified. For the marine omega-3 fatty acids group, a major CVD event occurred in 386 participants, the corresponding number in the placebo group was 419 (RR 0.92; 95 % CI 0.80–1.06;  $p=0.24$ ). In the analyses of key secondary end points, the RRs for the expanded composite endpoint of CVD, 0.93 (95 % CI 0.8–1.04); for total MI, 0.72 (95 % CI 0.59–0.90); for total stroke, 1.04 (95 % CI 0.83–1.31); for death from CVD causes, 0.96 (95 % CI 0.76–1.21). No excess risks of bleeding or other serious adverse events were observed. Although, more results are expected and other trials are under way, it seems sensible to conclude that vitamin and mineral supplements cannot match all the biologically active compounds present in food, and cannot compensate for an unhealthy diet.

## Conclusions

Current evidence is most consistent with that high consumption of fruits, vegetables, and whole grains and low processed (sodium-preserved) meat consumption may lower the risk of CVD. The PREDIMED trial provides support that a Mediterranean diet, enriched with extra-virgin olive oil or nuts, reduces CVD risk. It has been estimated that a suboptimal diet (e.g. suboptimal intake of fruits, vegetables, and whole grains and high sodium intake) accounts for about 50 % of deaths from CHD and stroke (Micha et al. 2017). Consumption of other foods and beverages rich in phenolic compounds, such as chocolate, coffee, and tea has been found to be inversely associated with risk of CVD, but the causality of these associations is unclear as RCTs corroborating these relationships are unavailable. Other foods, such as potatoes, refined grains, legumes, dairy products, and eggs generally appear neutral for CVD.

A limitation of available evidence is that most findings come from observational studies, which are susceptible to confounding and reverse causality. Moreover, measurement errors in the assessment of dietary intake and changes in diet during follow-up could have influenced (most likely attenuated) the results.

Overall, current evidence indicates that the best means to reduce CVD risk is to follow a Mediterranean- or DASH-like diet abundant in fruit, vegetables and whole grains (i.e. foods rich in essential nutrients and phenolics), and reduced in processed meat, sugar and salt. Moreover, there is currently very little evidence demonstrating that dietary supplements reduce the risk of CVD either for primary or secondary prevention.

## Research needs

- More long-term intervention studies of single foods or total diets are desirable to fully support the evidence from observational epidemiology.
- There is a need to further assess the potential link between food additives and CVD, and to better understand the consequences of frequent consumption of high and ultrahigh processed foods in relation to CVD health.
- Emerging diet-related less explored factors are those related to the microbiome.

Table 2. Results from meta-analyses of prospective studies of dietary patterns, foods, and beverages in relation to risk of cardiovascular disease.

Exposure	Comparison	Coronary heart disease		Stroke		Heart failure		Refs.
		No.*	RR (95 % CI)	No.*	RR (95 % CI)	No.*	RR (95 % CI)	
Mediterranean diet	Highest vs. lowest category	11	0.70 (0.62–0.80)	6	0.73 (0.59–0.91)	1	0.79 (0.68–0.93)	a–b
DASH diet	Highest vs. lowest category	3	0.79 (0.71–0.88)	3	0.81 (0.72–0.92)	2	0.71 (0.58–0.88)	c
Fruit and vegetables	Per 200 g/day increase	15	0.92 (0.90–0.94)	10	0.84 (0.76–0.92)	3	0.99 (0.82–1.18) <sup>†</sup>	d,e
Whole grains	Highest vs. lowest category	7	0.85 (0.81–0.90)	7	0.91 (0.82–1.02)	5	0.91 (0.85–0.97)	d
Nuts	Per 28 g/day increase	11	0.71 (0.63–0.80)	11	0.93 (0.83–1.05)	2	1.09 (0.97–1.22)	d,f
Chocolate	Highest vs. lowest category	6	0.90 (0.82–0.97)	5	0.81 (0.73–0.90)	5	0.86 (0.82–0.91) <sup>‡</sup>	g,h
Dairy products	Highest vs. lowest category	13	0.99 (0.92–1.07)	12	0.96 (0.90–1.01)	3	1.00 (0.90–1.10)	d
Egg	Per 50 g/day increase	9	1.00 (0.95–1.06)	10	0.99 (0.93–1.05)	4	1.16 (1.03–1.31)	d
Fish	Per 100 g/day increase	15	0.88 (0.79–0.99)	15	0.86 (0.75–0.99)	7	0.80 (0.67–0.95)	d
Red meat	Per 100 g/day increase	3	1.15 (1.08–1.23)	7	1.12 (1.06–1.17)	4	1.08 (1.02–1.14)	d
Processed meat	Per 50 g/day increase	3	1.27 (1.09–1.49)	6	1.17 (1.02–1.34)	2	1.12 (1.05–1.19)	d
Sweetened beverages	Per 250 ml/day increase	4	1.17 (1.11–1.23)	6	1.07 (1.02–1.12)	NA	NA	d
Coffee	3–4 cups/day vs. none	30	0.90 (0.84–0.97)	11	0.83 (0.74–0.92)	5	0.90 (0.82–0.99)	i–k
Tea	Per 3 cups/day increase	7	0.73 (0.53–0.99)	7	0.82 (0.73–0.92)	NA	NA	l
Alcohol								
Light	<1 drink/day vs. none	9	0.75 (0.65–0.88)	20	0.90 (0.85–0.95) <sup>§</sup>	12	0.86 (0.81–0.91)	m,n
Moderate	1–2 drinks/day vs. none	15	0.66 (0.59–0.75)	20	0.92 (0.87–0.97) <sup>§</sup>	11	0.88 (0.77–1.01)	m,n
High	3–4 drinks/day vs. none	9	0.67 (0.56–0.79)	21	1.08 (1.01–1.15) <sup>§</sup>	10	0.91 (0.80–1.04)	m,n
Heavy	>4 drinks/day vs. none	9	0.76 (0.52–1.02)	12	1.14 (1.02–1.28) <sup>§</sup>	4	1.16 (0.92–1.47)	m,n

Abbreviations: CI, confidence interval; DASH, Dietary Approaches to Stop Hypertension; NA, not available; RR, relative risk.

\*Number of prospective studies included in the meta-analysis.

<sup>†</sup>Results are for vegetables only and for the highest vs. lowest category.

<sup>‡</sup>Results are for low-to-moderate (<7 servings/week) vs. no chocolate consumption.

<sup>§</sup>Results are for ischemic stroke. Light and moderate alcohol consumption was not associated with intracerebral haemorrhage or subarachnoid haemorrhage but heavy drinking was associated with increased risk with RRs of 1.67 (95 % CI 1.25–2.23) and 1.82 (95 % CI 1.18–2.82), respectively (Larsson et al. 2016d).

a) Rosato et al. 2017, b) Tektonidis et al. 2015 and 2016, c) Salehi-Abargouei et al. 2013, d) Bechthold et al. 2017 e) Aune et al. 2017, f) Aune et al. 2016b, g) Larsson et al. 2012a and 2016c, h) Gong et al. 2017, i) Ding et al. 2014, j) Larsson and Orsini 2011b, k) Mostofsky et al. 2012. l) Zhang et al. 2015, m) Ronksley et al. 2011, n) Larsson et al. 2016d and 2017c

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## 4. Persistent organic pollutants and cardiovascular disease

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### Introduction

CVD is multi-factorial and growing evidence suggests that environmental contaminants are important and potentially preventable CVD risk factors. This chapter will summarize some epidemiological evidence on CVD risk mainly in relation to population background exposure to halogenated persistent organic pollutants (POPs) as identified under the Stockholm Convention on POPs (UNEP 2001) and with focus on the postnatal exposure situation. It is not an aim of this chapter to review all available literature in a systematic manner. Instead, the chapter will integrate and summarize information from the regulatory side with state-of-the-art information from observational, toxicological, and mechanistic studies, deriving new synthesized knowledge and more in depth understanding of the role that food-derived POPs may play in CVD development. Critical knowledge gaps and research needs are highlighted to allow for the identification of disease prevention opportunities of relevance for public health. Evidence-based knowledge on POPs exposures is of importance for accurate health risk assessments, balancing of benefits and risks of the consumption of certain foods, and for the implementation of appropriate health protection guidelines and recommendations. Evidence-based POPs knowledge is also important for correct restrictions on POPs' emissions and uses.

### POPs – compounds included and how we are exposed

Individual compounds and compound groups identified as POPs under the Stockholm Convention are targeted for elimination or reduction because of their toxicological properties in biota, their persistence and bioaccumulation potential in the environment and in living organisms, and their wide global distribution. The chlorinated POPs, which include dioxins, polychlorinated biphenyls (PCBs) and organochlorine (OC) pesticides, are among the most widely dispersed and most concerning POPs. The dioxins and PCBs comprise large numbers of individual compounds. Dioxins are grouped into the categories polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) and PCBs into dioxinlike and non-dioxinlike PCBs. OC pesticide-POPs include individual compounds such as the fungicide hexachlorobenzene (HCB), the insecticide dichlorodiphenyltrichloroethane (DDT) and its main persistent metabolite *p,p'*-dichlorodipenyldichloroethylene (DDE). Many chlorinated POPs with large former commercial productions and uses, such as PCBs and DDT, are being phased out from industrial and commercial production and uses since the late 1970s. In parallel, since the 1980s, technical processes generating some chlorinated POPs, such as dioxins, have been and continue to be strictly regulated to reduce by-product formation and associated unintended environmental emissions.

In addition to the chlorinated POPs, the Convention also captures brominated and fluorinated POPs, such as the brominated flameretardants (BFRs), and the perfluoroalkyl and polyfluoroalkyl substances (PFAS). BFRs and PFAS are industrial chemicals in current production and frequently used in numerous common consumer products. More than 3,000

different PFAS are currently on the market. In contrast, only a few individual compounds of these commercial classes of chemicals have been identified and listed as POPs (Stockholm Convention 2019). Examples are perfluorooctane sulphonate (PFOS), perfluorooctanoic acid (PFOA), a handful of polybrominated diphenyl ethers (PBDEs), as well as hexabromocyclododecane (HBCDD).

Compared with high-dose exposure in occupational or accidental settings, background exposure to POPs in the general population is characterized by low-dose and long-term – mostly lifelong exposure. Chlorinated and brominated POPs bioaccumulate and build up in the food chain over time and, once ingested, persist for a long time in body fat. Diet is the main source of exposure to chlorinated POPs, with meat, fish, and dairy products as important contributors to total intake (Schechter et al. 2010; Bergkvist et al. 2012). Likewise, humans are currently exposed to PFAS in daily life, mainly through the diet, with fish and seafood as important sources (Domingo et al. 2017), but also drinking water and indirect contamination from food packaging materials or cookware could be important (Bowman 2015). In addition to body fat, these fluorinated compounds end up bound to the protein components in blood. Consequently, despite regulatory activities to decrease and limit the environmental exposure, POPs derived from food and feed continue to be detected in human adipose tissue, blood and breast milk (Pumarega et al. 2016).

Currently, large segments of the populations are being exposed to background dioxin and PCB levels that are exceeding the tolerable weekly intake (TWI) levels recommended by the European Food Safety Authority (EFSA) (EFSA 2018a). For PFOAS and PFOA, the evaluation by EFSA in 2008, identified clear safety margins between exposure- and effect-concentrations (EFSA 2008a), while in their recent evaluation, only small or non-existing safety margins could be identified for these compounds. As a result, EFSA established markedly decreased TWI values for PFOS and PFOA (EFSA 2018b); values, which will remain preliminary until EFSA has completed its evaluation of the whole PFAS-group as expected during 2019.

POPs derived from food and feed therefore continue to be of concern from a human health perspective, especially because health outcomes linked to POPs are observed at even lower exposure levels as more health data is being collected and knowledge increase. For instance, previous high global and local emissions of chlorinated POPs have direct consequences on today's restrictions of fish consumption for children and women ever planning to get pregnant in Sweden, as well as on societal costs of food and feed biomonitoring programs across Europe.

### Dioxins and PCBs

Dioxins and PCBs are highly persistent and lipophilic POPs, which accumulate in the food chain. As a result, there is a pronounced body burden increase in humans over the life-course (Bjerma et al. 2013). Since dioxins and PCBs are hydrophobic, they generally do not occur in drinking water or food of plant origin at levels of health concern. From a chemical point of view, dioxins and PCBs comprise large numbers of individual compounds, i.e. 75 PCDDs, 135 PCDFs, and 209 PCBs, which always are present as mixtures in the environment and human tissues. Among the PCBs, 12 congeners have dioxin-like properties and the remaining 197 PCBs are referred to as non-dioxin-like. The grouping of PCB congeners is largely reflecting the number and position of the chlorine atoms, which gives individual PCB congeners different

biological activity and different toxicological profile. Congeners with a structure similar to that of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the most potent dioxin, are able to activate the aryl hydrocarbon receptor (AhR) with high potency, similar to the twelve most toxic dioxin molecules. The non-dioxin-like PCBs, on the other hand, do not bind or activate AhR in a high potency-manner, but instead bind to and activate the constitutive androstane receptor (CAR) and/or the pregnane X receptor (PXR) (Elabbas et al. 2013; JECFA 2016). Current understanding points towards key roles of AhR, CAR, and PXR in normal physiology as well as in POPs toxicology and mode-of-action. The physiological roles of these nuclear receptors entail that they are involved in numerous cellular functions across organ systems throughout life, including early development of the cardiovascular system as well as associated organs, e.g. the immune and nervous systems (Moore et al. 2016; Zhou 2016; Cheng et al. 2017). Key elements of AhR, CAR, and PXR functioning are via regulatory involvement in the homeostatic control of nuclear receptor signaling molecules. There is, thus, the opportunity for dioxins and PCBs to induce a wide range of health effects, which are due to altered overall and cellular metabolism of signaling molecules, such as lipids (e.g. fatty acids and cholesterol), hormones (e.g. estrogen, androgen and thyroid hormones), vitamins (e.g. retinoic acid and vitamin D), and bile acids. Appropriate cellular and circulating concentrations of these endogenous molecules are all of high relevance for the cardiovascular system.

Initial epidemiological and case studies on dioxins identified epidermal, systemic, neurological, and psychiatric outcomes following occupational and accidental exposure situations with no attention to CVD (WHO 1998). In 2017, the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) reviewed the epidemiological studies of occupational exposure to chemicals and CVD. They concluded, based on 5 studies, that there is moderately strong (the highest level of evidence for observational studies) evidence for a causal association between exposure to phenoxy herbicides contaminated during production with TCDD and heart disease (SBU 2017). In 2018, EFSA (EFSA 2018a) published a comprehensive health risk assessment on dioxins and dioxin-like PCBs based on predefined science-based regulatory target questions using a systematic review approach with strict inclusion criteria and evaluation of bias for each selected study. The individual studies included in the EFSA CVD evaluation were appraised for sufficient reliability and consisted mainly of occupationally exposed individuals. Analysed outcomes in these selected studies were mainly limited to the assessment of CVD mortality; further, very few studies demonstrated an overall low risk of bias and adequate power (EFSA 2018a). Thus, based on a limited number of studies and outcomes the EFSA evaluation concluded that the strongest support for increased risk of CVD following dioxin exposure came from a study of occupational exposure at a very high exposure level, i.e. compared to population-based background exposure levels (Steenland et al. 1999). Results from CVD outcome studies conducted in the general population with lower exposure levels to dioxin were considered inconsistent.

Experimental studies with dioxins and PCBs in cell and postnatal animal models support cardiovascular findings in humans. These studies show that dioxins and PCBs induce cellular responses, including acute and chronic inflammation, oxidative stress, disruption of lipid metabolism and endocrine homeostasis, as well as deregulation of cytochrome P450 enzymes. All of these cell responses are of high relevance for the cardiovascular system and represent well-known risk factors for CVD (Andersson et al. 2011; Arsenescu et al. 2011; Dalton et al.

2001; Eske et al. 2014; Helyar et al. 2009; Liu et al. 2015; Lind et al. 2004; Kopf et al. 2008). POP's inflammatory and oxidative effects may be induced by impairment of mitochondrial function, since mitochondria is a target of environmental toxicants (Meyer et al. 2013). Mitochondria is considered to be the major site of intracellular reactive oxygen species (ROS)-formation (Brand et al. 2016), and OC pesticides are known to impair mitochondrial function in hepatocytes and aggravated disorders of fatty acid metabolism, especially DDT (Liu et al. 2017, Song et al. 2008).

### PFAS

PFAS is a very large group of manufactured fluorinated chemicals of which some have been produced since the 1950s. Due to their unique amphiphilic characteristics – including water and oil repellence and thermal stability, as well as, their film forming and surfactant properties – they have leaked into the environment. The unique physico-chemical properties of PFAS make them extremely useful in e.g. surfactants, lubricants, polishes, paper and textile coatings, food packaging and fire-retarding foams (Lau et al. 2007). These same properties make them extremely persistent in the environment and in living organisms. As an example, the elimination half-life range in humans for PFAS has been reported to be 3.8–8.5 years (Olsen et al. 2007; Stableski et al. 2017).

PFAS have structural similarities with fatty acids and may interfere with their metabolism (Frayn et al. 1996; Pilz et al. 2006). PFAS also activate the peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ), which is expressed predominantly in the liver, heart and endothelial cells and whose endogenous ligands are fatty acids. PPAR $\alpha$  is a major regulator of a wide variety of target genes involved in lipid metabolism (Rosen et al. 2008; Ren et al. 2009; Berger et al. 2005; Barger et al. 2000). PFAS may interfere with the signaling pathways of energy metabolism and blood pressure regulation and have been associated with oxidative stress and endothelial dysfunction; there are all linked with each other and considered important intermediary events in the aetiology of CVD. Recent molecular biology knowledge supports that additional nuclear receptor pathways, e.g. LXR, FXR, RXR, and RAR, are involved with PFAS-induced modulations of cholesterol, as well as, steroid hormone homeostasis. Likewise, current understanding points to CAR and PXR as being involved with the PFAS mode of action.

Most studies of rodents exposed to high concentrations of PFOA, although not all (Rebholz et al. 2016), have resulted in reduced blood concentrations of total cholesterol and triglycerides through altered expression of lipid metabolism related genes.

### POPs exposures and risk of cardiovascular disease

This section summarizes up-to-date epidemiological evidence on a selected number of chlorinated and fluorinated POPs regarding their associations with the CVD outcomes mortality, IHD, stroke, and other CVD pathologies, as well as the CVD risk factors hypertension and hyperlipidemia. Most of the existing literature regarding CVD risk and POPs exposure is on chlorinated POPs, and to a lesser extent on fluorinated POPs. Thus, when PFAS are not mentioned for a specific outcome in this section it is to be understood that there were no retrieved studies on PFAS to refer to. For the chlorinated POPs, focus in the below text is

on studies on dioxins and PCBs, with just occasional data on the OC pesticides. For PFAS, focus is mainly on studies assessing PFOS and PFOA.

### Cardiovascular mortality

#### *Dioxins, PCBs, OC pesticides, and PFAS*

The first human evidence on POPs and their cardiovascular toxic effects was in workers or residents near accidental spills highly exposed to POPs. As mentioned, in the EFSA health risk assessment on dioxin (EFSA 2018a), the strongest support for increased risk of CVD (focusing on CVD mortality) came from very high occupational exposure, while the results were inconsistent at lower exposure levels. CVD mortality in the population living in the area of the Seveso accident, which was highly exposed to TCDD, showed increased CVD mortality only during the first years after the accident (Consonni et al. 1976). In a cohort study of Swedish workers, mortality from CVD was significantly increased among those employed for more than five years in high PCB-exposed jobs, calculated with a latency of 20 years (Gustavsson and Hogstedt 1997).

Only a few population-based studies have evaluated POP levels and CVD mortality. In a prospective study (mean follow-up 4.1 years) of men and women aged 70 or over included in the 1999-2004 US National Health and Nutrition Examination Survey (NHANES), higher exposures to different PCBs were associated with 2 to 3-fold higher risk of CVD mortality (only in those with low fat mass though). OC pesticides showed patterns of associations similar but weaker than with PCBs (Kim et al. 2015). However, in a similar later study, based on data from the 1999-2011 NHANES (mean follow-up 6.4 years), serum measurements of neither OC pesticides, PCBs, PBDEs, nor PFAS were clearly associated with cardiovascular mortality (Fry and Power 2017). In a recently published population-based cohort study (follow-up period of 10 years), elevated levels of highly chlorinated PCBs were associated with increased mortality, mainly from CVD. No significant associations were observed for OC pesticides and PBDEs (Lind et al. 2019).

### Ischemic heart disease

#### *Dioxins and PCBs*

Vietnam veterans who were occupationally exposed to Agent Orange – a mixture of herbicides and TCDD – experienced a higher risk of heart disease, odds ratio (OR) 1.52 (CI 95 %: 1.18–1.94) compared with veterans who did not handle the herbicide (Kang et al. 2006). Likewise, a study identifying the major contaminant waste sites in New York showed that patients living in areas contaminated with POPs had a statistically significant 15 % increased hospital discharge rate of IHD and 20 % of MI specifically, compared with those living in non-contaminated areas (Sergeev and Carpenter 2005).

Validated estimates of dietary PCB exposure have been assessed in the Swedish mammography cohort (SMC) and the Cohort of Swedish Men (COSM) – two population-based prospective cohorts including >70,000 women and men. Dietary PCB exposure was associated with a 60–70 % statistically significant higher risk of MI (Bergkvist et al. 2015 and 2016). In the analyses exploring whether factors related to the retention of PCBs in the body modified the subsequent

risk of MI, the association appeared stronger in lean than overweight and obese men and women. A similar tendency of a stronger association was observed in nulliparous women when compared to those with one or more children. Possible explanations could be higher concentrations of circulating PCBs observed in blood of lean than of obese because of the lower dilution of PCBs in adipose tissue; and the transplacental and lactational transfer of PCBs during pregnancy and breastfeeding, resulting in a lower body burden of PCBs in multiparous than nulliparous women.

### *PFAS*

For PFAS, no association was observed with IHD either among workers at a Mid-Ohio Valley chemical plant (Van den Berg 2006) or in older male anglers in Wisconsin with high fish consumption (Christensen et al. 2016; Winquist and Steenland 2014). Likewise, in a nested case-control study among Swedish farmers and rural residents only one PFAS (perfluoroheptanoic acid; PFHpA) out of eight PFAS measured in the study was associated with increased risk of IHD (Mattsson et al. 2015).

### Stroke

#### *Dioxins, PCBs and OC pesticides*

Residency in ZIP code areas containing or abutting environmental sources of POPs was also associated with a statistically significant 13 % increased risk of being hospitalized for a stroke with comorbid hypertension (Sergeev and Carpenter 2011). A prospective study was performed with the elderly participants from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS), where twenty-one POPs were measured in plasma collected at baseline. After a 5-year follow-up, most PCBs with 4, 5, or 6 chlorine atoms, dioxins and OC were significantly associated with risk of stroke (validated by hospital records); the adjusted ORs for values  $\geq$ 90th percentile of the summary measures were 5.5 (CI 95 % 1.7–18.1) for PCBs and 4.0 (1.1–14.6) for OC pesticides (Lee et al. 2012).

In the above-mentioned population-based prospective Swedish cohorts SMC and COSM, significant increases in risk for both ischemic and haemorrhagic stroke were observed with higher dietary PCB exposure in women (Bergkvist et al. 2014) but only for haemorrhagic stroke in men (Kippler et al. 2016). An almost three-fold higher risk of haemorrhagic stroke was observed in both genders, comparing extreme quartiles of dietary exposure to PCBs. In line with the results for MI, indications of higher dietary PCB-associated risks of total stroke in women were observed among lean as compared to overweight/obese and among those with few children (0–1) as compared to those with more. Additionally, women born after 1931, when the commercial production of PCB started, likely leading to prenatal exposure, showed associations with higher risk than those born before the production started (p for interaction on the multiplicative scale 0.11) ((Bergkvist et al. 2014).

## Other cardiovascular pathologies

### *Dioxins and PCBs*

In a cross-sectional assessment of 70-year-old men and women from Uppsala, Sweden, several individual PCBs were associated with the presence of carotid artery plaques. Some of the highly chlorinated PCBs were also associated with the echogenicity of the intima-media complex, a marker of vascular wall composition (Lind et al. 2012).

Obese subjects from the NHANES (1999–2004) with PAD (based on an ankle brachial index <0.9) had significantly increased mean lipid-standardization value of the sum of OC pesticides (OR 1.19; 95 % CI 1.07–1.33) (Min et al. 2011). In the prospective Swedish cohorts SMC and COSM, dietary exposure to PCBs was associated with a 1.48 (95 % CI 1.12–1.96) RR of heart failure in women and 1.42 (95 % CI 1.08–1.86) RR in men, comparing extreme quintiles (Åkesson et al. 2019).

### *PFAS*

In a population-based cross-sectional study of young adults, a positive relationship between PFOS and IMT was found, but this relationship was inverse for the perfluoroundecanoic acid (PFUnDA) and no association was observed for other PFAS (Lin et al. 2013). Similarly, in a cross-sectional analysis within the PIVUS, overall, no associations were observed between PFAS and markers of atherosclerosis (i.e. IMT, the echogenicity in the intima-media complex [a marker of lipid infiltration in the artery] and occurrence of carotid plaques) (Lind et al. 2017). In this same cohort, however, when this assessment was conducted using a longitudinal approach (10-year follow-up), changes in plasma levels of several PFAS were positively related to the increase in IMT (Lind et al. 2018). Likewise, also in PIVUS, several of the PFAS, especially perfluorononane acid (PFNA), have been linked to myocardial geometry: a reduction in relative wall thickness and an increase in left ventricular diameter (Mobacke et al. 2018). These findings may indicate that PFAS might both interfere with the atherosclerotic process and have a role in cardiac remodeling.

## POPs exposures and cardiovascular disease risk factors

High blood pressure (hypertension), raised blood lipids (hyperlipidemia), visceral obesity and impaired glucose tolerance (diabetes mellitus) are metabolic conditions closely linked to cardiovascular risk, which have been associated with blood concentrations of chlorinated and fluorinated POPs. There is also experimental evidence connected to these CVD risk factors/conditions; particularly for hypertension and hyperlipidemia, which are associated to the atherosclerosis process.

## Hypertension

### *Dioxins, PCBs and OC pesticides*

Studies have observed higher prevalence of hypertension in populations highly exposed to POPs (Goncharov et al. 2011; Huang et al. 2006; Valera et al. 2013). The few available observational studies on the general population considering this potential link, however, have



reported somewhat discordant results (Donat-Vargas et al. 2015; Mustieles et al. 2017; Park et al. 2016a). The most recent meta-analysis published on POP levels in human plasma and hypertension risk in the general population (Park et al. 2016b) observed a pooled OR of hypertension, comparing extreme categories, of 1.45 (95 % CI 1.00–2.12) for the sum of dioxin-like PCBs and 1.10 (95 % CI 1.03–1.18) for DDE. The OR for the sum of non-dioxin-like PCBs did not reach statistical significance, and there were not enough studies for HCB.

In the Västerbotten Intervention Programme (VIP) study with two blood samplings and blood pressure measurements, 10 years apart, plasma DL-PCBs and DDE, but neither NDL-PCBs nor HCB, were recently observed to be associated with hypertension. Only the association for DL-PCBs remained statistically significant after lipid-standardization and adjustment for body mass index and total serum lipids. The multivariable-adjusted OR of hypertension based on repeated measurements was 1.52 (95 % CI 1.08–2.13) for dioxin-like PCBs (third vs. first tertile of lipid-standardized POPs) (Donat-Vargas et al. 2018).

*In vitro* (Andersson et al. 2011; Eske et al. 2014; Helyar et al. 2009; Liu et al. 2015) and animal (Arsenescu et al. 2011; Lind et al. 2004; Kopf et al. 2008; Dalton et al. 2001) evidence reveals that dioxin-like PCBs induce chronic inflammation, dysfunction in the vascular endothelium and may disturb lipid metabolism (Lind et al. 2004; Dalton et al. 2001), potentially leading to the formation of atherosclerotic plaques (Henning et al. 2007), through different AhR-mediated pathways such as via expression of several inflammatory markers (Eske et al. 2014; Liu et al. 2015) or increasing cellular oxidative stress (Kopf et al. 2008). The dioxin-like PCB congener 126 showed to stimulate the production of vasoconstriction factors, including cyclooxygenase (COX-2), prostaglandins and ROS, as well as to inhibit the release of the vasodilator nitric oxide (NO) (Andersson et al. 2011; Helyar et al. 2009). Experimental or animal studies considering the biological mechanism for potential non-dioxin-like-PCB-induced cardiovascular effects are still lacking.

The DDE's anti-androgen activity might be a likely mechanism whereby DDE disturbs the blood pressure. Low testosterone levels have been linked to hypertension (Akishita et al. 2010), and DDE levels showed to be inversely related to testosterone levels (Blanco-Munoz et al. 2012). Experimental evidence suggests that DDT can act on several arms of the renin-angiotensin system to possibly increase risk of hypertension (Davis et al. 1972).

### *PFAS*

As regards blood pressure, PFOA was associated with higher prevalence of hypertension in U.S. NHANES (Min et al. 2012), but this was not confirmed by two subsequent prospective studies (Winqvist et al. 2014; Geiger et al. 2014) and even an inverse association has been reported (Christensen et al. 2016). In the VIP study, PFAS appeared not to be associated with hypertension (Donat-Vargas et al. 2018).

We found only one *in vitro* (Qian et al. 2010) and one animal (Cui et al. 2009) study suggesting a plausible link between PFAS and vascular injury and hypertension. PFAS' interference with the signaling pathways of the thyroid hormones (Lau et al. 2007; Butenhoff et al. 2002) – involved in energy metabolism and blood pressure regulation – might be another mechanism of action of PFAS. Moreover, PFAS exposure has been associated with oxidative stress (Yao and Zhong 2005; Liu et al. 2007) and endothelial dysfunction (Qian et al. 2010; Hu et al. 2003), both connected to the development of CVD.

## Hyperlipidemia

### *Dioxins and PCBs*

Chlorinated POPs are fat-soluble hydrophobic molecules, and consequently, elevated blood lipids tend to carry proportionally higher POP concentrations, which makes it difficult to address the association between lipophilic POPs and disturbances in lipid metabolism (Goncharov et al. 2008; Arrebola et al. 2014).

Experimental evidence shows that dioxin-like PCBs may disturb lipid metabolism (Lind et al. 2004; Dalton et al. 2001). It has been reported that low-dose POP mixtures significantly affected the expression of critical genes involved in lipid homeostasis and ectopic fat accumulation in muscle and liver (Ibrahim et al. 2011). Several action mechanisms for how POPs may disturb lipid metabolism have been suggested such as the down-regulation of insulin-induced gene-1 (Insig-1) and Lpin1, two master regulators of lipid homeostasis (Ruzzin et al. 2010). Additionally, dioxin- and non-dioxin-like PCBs have been reported to induce P450 enzymes, causing an over-reactive liver that synthesizes increased levels of cholesterol and triglycerides (Goncharov et al. 2008).

### *PFAS*

The most consistently observed PFAS-associated health effect in humans (mainly for PFOA) is the increase in cholesterol (Winquist and Steenland 2014; Fitz-Simon et al. 2013; Steenland et al. 2010; Sunderland et al. 2018), opposite to what has been observed in rodents in most studies (Haughom and Spydevold 1992; Martin et al. 2007; Gugue et al. 2006; Loveless et al. 2006). EFSA concluded that epidemiological studies provide strong support for causal associations between exposure to PFOS and PFOA and increased serum levels of cholesterol and identified this as the critical effect (EFSA 2018b). In a recent population-based study among a group of non-diabetic VIP participants, there was no indication of any associations between PFAS and increased blood lipids. In contrast, PFAS were consistently associated with lower levels of triglycerides. For total cholesterol, the associations were not consistent and considered inconclusive (Donat-Vargas et al. 2019). The hazard profile of individual PFAS could vary depending on chain length, functional groups and on species (Wolf et al. 2008 and 2012). Human data on other longer-chain PFAS, introduced later than PFOA and PFOS, remain scarce.

Most studies of rodents exposed to high concentrations of PFOA, although not all (Rebholz et al. 2016), have resulted in manifest reduction in both total cholesterol and triglycerides through altered expression of lipid metabolism-related genes.

## Challenges in assessing the role of POPs exposures in cardiovascular disease

There are many critical knowledge gaps and multiple challenges involved with the assessment of associations between POPs and human health indicators. All of these challenges are relevant for the assessment of CVD risk. This paragraph summarizes challenges involved with the assessment of CVD risk in relation to exposure to mixtures of POPs and POP exposure via fish.

### Mixtures of POPs

Individuals accumulate mixtures of POPs and other persistent toxic substances throughout the life course. However, epidemiological studies have usually been performed focusing on specific POPs not tackling adequately the accumulation of multiple chemicals and not taking into account the existence of mixture effects (e.g. additive, synergistic, and antagonistic). Examining a mixture effect is complex and challenging. Nevertheless, it is important to properly identify the risk in order to implement relevant and appropriate evidence-based targeted interventions (e.g. banning specific compounds) and recommendations (e.g. limit values and tolerable intake levels). It has so far been difficult to comprehensively assess mixture exposures in the general population (Porta et al. 2012). Some statistical methods are deemed to be suitable for the study of mixture effects of environmental contaminants (Lampa et al. 2014) but still they have rarely been applied.

### The fish intake dilemma

Fatty fish constitutes the major source of POPs and PFAS exposure in some populations, but also of cardio-protective nutrients such as vitamin D and the long-chain omega-3 fatty acids, which may lower blood pressure and blood lipids concentrations, decrease inflammation and improve vascular function (Mozaffarian and Wu 2011). Since fishes with the highest fat content have the highest concentration of fat soluble nutrients (e.g. EPA-DHA and vitamin D) but also higher lipophilic contaminants, it may be hard to reach the recommended intake level of EPA-DHA without exceeding the POP exposure (Sioen et al. 2009). In the studies conducted in the SMC and COSM, EPA and DHA intakes were only associated with lower risk of CVD when accounting for a potential concomitant confounding by dietary PCB exposure (Bergkvist et al. 2014, 2015 and 2016; Kippler et al. 2016).

POP exposure through fish intake differs by countries due to differences in the type of fish consumed, the frequency and the contamination of the local water. Therefore, risk-benefit assessment of POPs and resultant national dietary guidelines on fish consumption and associated contaminants need to be specific by region. There is no doubt that net benefits of fish consumption can only be present when POPs contamination is reduced to a minimum. Current knowledge suggests that restricted emissions of manufactured chemicals with high persistence and bioaccumulation potential, such as PFAS, are needed to protect fish supplies also for next generations.

### Early life exposure and epigenetic changes

It has been recognized that environmental exposures during key stages of development, such as gestation and lactation, may have important effects on the epigenetic code. As a result, durable changes in gene expression patterns may even permanently alter the structure or function of specific organ systems. Worst case scenarios may include increased risk of metabolic disease later in life and even impaired health across generations (Grun and Blumberg 2006). Considering current molecular biology understanding of heart and vascular formation, it is conceivable to assume that the nuclear receptor-mediated effects of dioxins and PCBs on heart formation and vascularization may have impacts on the epigenome, in particular when exposure occurs in fetal life. Indeed, experimental data suggest that the developing heart is

sensitive to POPs exposures and that both structural and functional development can be impaired (Fang et al. 2016). Although these experimental findings are mostly derived from non-mammalian models, they are considered relevant also for the mammalian, including human, embryo-fetal exposure situation.

## Conclusions

POPs exposures continue to be of concern from a human health perspective; previous and current POPs emissions have direct consequences on today's food recommendations and societal costs of food and feed biomonitoring programs across Europe. The bioaccumulating properties of POPs will affect the exposure scenario also for coming generations. In the global work towards sustainable food production and environmental safety there is an urgent need to secure safe foods as well as drinking water supplies in terms of their POPs concentrations.

Despite some inconsistencies and research gaps (Lind and Lind 2018), there are plausible direct roles of chlorinated POPs in the development of CVD in the general population. Chlorinated POPs have also been associated with cardiovascular risk factors, including hypertension, while the fluorinated PFAS have mostly been related to lipid disturbances.

The potential cardiovascular risk derived from exposure to POPs is a concern for public health, since even a minor increased risk of CVD due to POPs exposures will have large population health impact because of the ubiquitous presence of POPs in food and feed in combination with the high population incidence of CVD.

## Current research challenges

To specifically advance knowledge about how POPs may contribute to CVD, there is a need to conduct well-designed prospective studies, preferably with serial (repeated) measurements and large sample sizes. In light of the inherent limitations of epidemiological studies, there is also a need for experimental studies, using real-world scenarios in terms of experimental models, doses, mixtures, and duration of exposures.

Specifically, POPs-CVD research challenges include:

- Identify combined effects as well as the contribution of individual POPs to specific aspects of CVD, including MI, ischemic and hemorrhagic strokes or atherosclerosis, and CVD risk factors such as hypertension and lipidemia.
- With new approaches, discriminate POP cardiovascular detrimental effects in humans from the cardiovascular benefits of nutrients naturally present in fish.
- Integrate metabolomics and other “omics” to better elucidate the molecular mechanisms involved and understand any gene-POPs interactions of importance for POP cardiovascular impact.
- Address developmental origin of CVD and the possible role of POPs exposure.

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## 5. Ambient air pollution

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### Introduction

Ambient air pollution is estimated to account for roughly 4.4 million premature deaths per year globally and is recognized as a leading cause of the global burden of disease (Cohen et al. 2017). Although contributing to several aspects of human disease, the greatest public health threat of air pollution is as a risk factor for CVD. Air pollution is composed of a mixture of particle matter with varying sizes, sources and toxicity as well as different gases such as nitrogen oxides (NO<sub>x</sub>), sulfur dioxide (SO<sub>2</sub>), carbon monoxide (CO), and ozone. Some of these pollutants are primary pollutants emitted directly from a source whereas others such as ozone, sulfate particles and nitrite particles are formed as secondary pollutants in complex interactions. The characteristics of these pollutants are heterogeneous, especially for particle matter pollution.

Particle matter (PM) is most frequently measured as mass concentration and subdivided into categories of aerodynamic diameter: ultrafine particles <0.1 μm (PM<sub>0.1</sub>), fine particles <2.5 μm (PM<sub>2.5</sub>), and inhalable particles <10 μm (PM<sub>10</sub>). Consequently, PM<sub>10</sub> contains coarse (2.5–10 μm), fine and ultrafine particles but are dominated by the mass of coarse and fine particles. Ultrafine particles are sometimes assessed as particle number concentration (PNC) since counts of particles are a good reflection of the amount of ultrafine particles. The composition of the air pollution mix will vary both spatially depending on sources and temporally depending on meteorological and seasonal factors.

The main sources of fine and ultrafine PM are combustion particles from traffic, power plants, industry, shipping and residential heating based on oil, coal or wood. In some parts of the world agricultural burning is also a large contributor to fine PM. Coarse particles are primarily the result of re-suspended road and soil dust from vehicles and construction but major contributions may also include desert dust in some areas. NO<sub>2</sub> and NO<sub>x</sub> primarily reflect combustion sources similar to PM<sub>2.5</sub> and ultrafine particles. SO<sub>2</sub> is emitted from combustion of fossil fuels such as coal and oil, however, levels have substantially reduced in Sweden and Europe where sulfur content in fuel has largely been removed.

Many pollutants, especially PM<sub>2.5</sub>, can travel suspended in air over very long distances (>100 km). Hence both local and distant emissions affect population exposure. Health effects of air pollution are generally expressed as associations between single pollutants and discrete health outcomes ignoring the interactions or effects of other co-pollutants. Multi-pollutant modelling and source apportionment have to a limited extent been employed to address this but still suffers from the strong correlations between pollutants and the time-space complexity of the air pollution mixtures. Consequently, observed associations for specific pollutants may reflect combined effects from several pollutants or proxy effects from correlated pollutants.

In this chapter we will briefly summarize the evidence regarding air pollution and CVD, go through important subclinical findings, and discuss possible mechanisms of action. Expert consensus reviews have been previously published for the AHA in 2004 and 2010 (Brook et al. 2004 and 2010), the European Society of Cardiology in 2015 (Newby et al. 2015), and the

WHO in 2013 (WHO 2013). Integrated scientific assessments specific to each individual air pollutant are also available at [www.epa.gov](http://www.epa.gov).

## Cardiovascular outcomes

### Total and cardiovascular mortality

Daily exposure to PM has been associated to non-accidental mortality in a multitude of studies across the globe. In a large meta-regression of European and North American studies called APHENA, a 10  $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{10}$  was associated with a 0.2–0.6 % higher all-cause mortality with slightly higher estimates for cardiovascular mortality among individuals  $\geq 75$  years old (Samoli et al. 2006). In meta-analysis of 110 time-series studies from all over the world, increased daily  $\text{PM}_{2.5}$  was associated with a 0.84 % (95 % CI 0.41–1.28 %) higher cardiovascular mortality per 10  $\mu\text{g}/\text{m}^3$  (Atkinson et al. 2014).

Short-term elevations in gaseous pollutants have also demonstrated associations with mortality in several large studies. Daily  $\text{NO}_2$  levels were associated with 0.4 % increased cardiovascular mortality per 10  $\mu\text{g}/\text{m}^3$  across 30 European cities (Samoli et al. 2006). The APHENA study also investigated short-term ozone levels and mortality and reported a 0.26 % (95 % CI 0.15–0.37 %) higher all-cause mortality per 10  $\mu\text{g}/\text{m}^3$  higher 1-hour daily maximum of ozone (Peng et al. 2013). Results were slightly higher for cardiovascular mortality in the same study.

Comparisons of exposure to air pollution between or within cities over the course of years in relation to mortality rates have been performed in several cohort studies adjusting for socioeconomic and individual factors. The first studies were performed in the US including the Harvard Six Cities Study (n=8,111) and the American Cancer Society Study (n= 500,000) demonstrating positive associations between living in cities with higher PM exposure and higher total mortality. Results for cardio-pulmonary mortality were stronger. In a systematic meta-analysis of long-term air pollution studies, including studies from Asia, a 10  $\mu\text{g}/\text{m}^3$  increase in long-term  $\text{PM}_{2.5}$  exposure was associated with a 6 % (95 % CI 4–8 %) higher cardiovascular mortality (Hoek et al. 2013). Since this review was published, results from the European Study of Cohorts for Air Pollution Effects (ESCAPE) encompassing a network of 22 European cohort studies including 4 from Stockholm, Sweden, published positive associations between annual  $\text{PM}_{2.5}$  averages and all-cause mortality (HR 1.07; 95 % CI 1.02–1.13 per 5  $\mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$ ) and non-significant associations with cardiovascular mortality (Beelen et al. 2014a and 2014b).

Long-term exposure to  $\text{NO}_2$  has also been positively associated with mortality. A meta-analysis of 23 publications reported a HR for all-cause mortality of 1.04 (95 % CI 1.02–1.06) per 10  $\mu\text{g}/\text{m}^3$  annual  $\text{NO}_2$  average (Faustini et al. 2014) in line with findings from the ESCAPE project (5.5 %; 95 % CI 3.1–5.0 %) (Beelen et al. 2014a). Moreover, results from the meta-analysis demonstrated that  $\text{NO}_2$  associations were independent of  $\text{PM}_{2.5}$  levels and reported higher risks for cardiovascular mortality, HR 1.13 (95 % CI 1.01–1.09) per 10  $\mu\text{g}/\text{m}^3$  increase in annual  $\text{NO}_2$  average.

Less research has been conducted on long-term ozone exposure and mortality. A meta-analysis of 14 publications from 8 cohorts concluded that there was no evidence for associations between ozone levels averaged over the whole year and mortality, however in 3 studies

providing estimates for the warm season 10 parts per billion (ppb) increase in ozone averaged in the warm season was positively associated with cardiovascular mortality (HR 1.01, 95 % CI 1.00–1.02) (Atkinson et al. 2016). In Stockholm, Sweden, a 10  $\mu\text{g}/\text{m}^3$  increase of ozone was associated with a 0.7 % increased risk of cardiovascular death (95 % CI 0.1–1.3 %) with stronger associations in individuals with a previous hospital admission for MI (Raza et al. 2018).

In sum, there is evidence to support associations between both short- and long-term exposure to air pollution and cardiovascular mortality. The evidence to support associations between air pollution and cardiovascular mortality is especially strong for PM followed by  $\text{NO}_2$  whereas the evidence of cardiovascular mortality from long-term exposure to ozone is primarily restricted to warm season in a few studies.

### Ischemic heart disease

Short-term exposures to air pollution has been investigated in relation to hospital admissions for IHD and acute MI both using time-series and case-crossover analyses. Some studies have demonstrated associations within as short as a few hours of exposure. In a systematic meta-analysis of 34 studies, several air pollutants were significantly associated with MI (RR per 10  $\mu\text{g}/\text{m}^3$  pollutant:  $\text{PM}_{10}$  1.006, 95 % CI 1.002–1.009;  $\text{PM}_{2.5}$  1.025, 95 % CI 1.015–1.036;  $\text{NO}_2$  1.011, 95 % CI 1.006–1.016; CO 1.048, 95 % CI 1.026–1.070;  $\text{SO}_2$  1.010, 95 % CI 1.003–1.017) (Mustafic et al. 2012). Only ozone did not demonstrate positive associations.

Fewer studies have been conducted investigating long-term exposure and incidence in IHD. Long-term exposure to  $\text{PM}_{10}$  was associated with a 12 % (HR 1.12; 95 % CI 1.12–1.25) higher risk of acute coronary events per 10  $\mu\text{g}/\text{m}^3$   $\text{PM}_{10}$  in roughly 5,000 participants in 11 European cohorts (Cesaroni et al. 2014). Other studies have not affirmatively demonstrated associations with  $\text{PM}_{10}$  (Puetz et al. 2008; Lipsett et al. 2011; Atkinson et al. 2013; Hoffmann et al. 2015). Long-term exposure to  $\text{PM}_{2.5}$  was associated with incidence of IHD (21 % per 10  $\mu\text{g}/\text{m}^3$  [95 % CI 4–42 %]) in the large Womens' Health Initiative based on 65,000 post-menopausal women (Miller et al. 2007) comparing exposures between cities. Stronger associations were observed in contrasts within cities. The ESCAPE study reported non-significant associations for  $\text{PM}_{2.5}$  but with effect sizes similar to those for  $\text{PM}_{10}$  and to the Womens' Health Initiative. Two analyses of the Worcester Heart Attack Study, using different methodologies of  $\text{PM}_{2.5}$  exposure assessment, also reported associations with incident IHD (Tonnet et al. 2009; Madrigano et al. 2013). However other studies did not observe associations between  $\text{PM}_{2.5}$  and incident IHD (Lipsett et al. 2011; Hoffmann et al. 2015; Puetz et al. 2009). A large administrative study from Vancouver, Canada, lacking many individual-levels confounders but with a similarly low pollution setting such as Sweden, reported positive associations between black carbon exposure assessed by land-use regression and incident IHD in contrast to our results (Gan et al. 2011). Comparatively fewer studies have been conducted regarding long-term exposure to gaseous pollutants and IHD. In a large administrative cohort in England  $\text{NO}_2$  was not significantly associated with incident MI whereas  $\text{SO}_2$  was positively associated (Atkinson et al. 2013). In Stockholm,  $\text{NO}_2$  was not associated with incident MI overall, but positive associations were observed for fatal MIs, especially those occurring outside of hospitals (Rosenlund et al. 2006).

There is quite robust support for positive associations between short-term PM,  $\text{NO}_2$ ,  $\text{SO}_2$  and carbon monoxide (CO) exposure and incident IHD. There is some paucity of studies focusing

on long-term air pollution exposure and incident IHD, however there is relatively strong evidence of associations with incident IHD for long-term PM exposure.

### Heart failure

Increases in daily averages of PM were associated with higher risk of hospitalization for heart failure in a meta-analysis of 35 studies. A 10  $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{2.5}$  was associated with 2.12 % (95 % CI 1.42–2.82 %) higher risk of hospitalization, similar to the risk observed for  $\text{PM}_{10}$  (1.63 % per 10  $\mu\text{g}/\text{m}^3$ , 95 % CI 1.20–2.07 %). Daily averages of  $\text{NO}_2$ ,  $\text{SO}_2$  and CO but not ozone were also associated with hospital admissions for heart failure ( $\text{NO}_2$  1.7 % per 10 ppb, 95 % CI 1.25–2.16 %;  $\text{SO}_2$  2.36 % per 10 ppb, 95 % CI 1.35–3.38 %; CO 3.52 % per 1 part per million (ppm), 95 % CI 2.52–4.52 %) (Shah et al. 2013).

Very few studies have investigated long-term exposure to air pollution in relation to heart failure. Both long-term averages of PM and  $\text{NO}_2$  were associated with incident heart failure in a large cohort of English general practices (HR 1.06 per 3.0  $\mu\text{g}/\text{m}^3$   $\text{PM}_{10}$ , 95 % CI 1.01–1.11 and similar HR for a 10.7  $\mu\text{g}/\text{m}^3$  increase in  $\text{NO}_2$ ) (Atkinson et al. 2013).

In the Multi-Ethnic Study of Atherosclerosis, a 5  $\mu\text{g}/\text{m}^3$  higher annual  $\text{PM}_{2.5}$  average was associated with a 4.0 g/m greater left ventricular mass index (95 % CI 0.3–8.2) in black Americans investigated with magnetic resonance imaging of the heart (Hicken et al. 2016). Similar associations were observed for  $\text{NO}_2$  and  $\text{NO}_x$  but no associations were seen in white Americans and no associations were observed for left ventricular ejection fraction. In another analysis of the same cohort  $\text{NO}_2$  was associated with greater right ventricular mass and larger right ventricular end-diastolic volume (Leary et al. 2014). These results reflect an increased cardiac workload in relation to air pollution perhaps reflecting effects of air pollution on increased pulmonary and systemic vascular resistance. In an experimental design of controlled human exposure to diesel exhaust during 2 hours, increased pulmonary vascular resistance was observed at high cardiac output, supporting the previous findings (Wauters et al. 2015). Higher residential long-term averages of  $\text{PM}_{2.5}$  and  $\text{NO}_x$  were associated with higher left atrial volume index measured with echocardiography in elderly women (Ohlwein et al. 2016). In addition, studies in mice have demonstrated several cellular and structural changes consistent with incipient heart failure after 9 months of exposure to  $\text{PM}_{2.5}$  compared to filtered air (Wold et al. 2012) and exacerbated angiotensin II-induced cardiac hypertrophy via a Rho-kinase dependent pathway after 3 months of exposure (Ying et al. 2009).

Overall there is a large body of evidence supporting associations between short-term exposure to air pollution and hospitalizations for heart failure both for PM and gaseous pollutants. While there are very few available studies, long-term exposure to PM and  $\text{NO}_2$  have demonstrated associations with incident heart failure and structural changes in heart function lending support to their contribution to heart failure.

### Stroke

Several studies have investigated short-term exposure to air pollution and stroke and have been summarized in several reviews. In a meta-analysis including 94 studies from 28 countries and 6.2 million strokes, daily increases in  $\text{PM}_{10}$ ,  $\text{PM}_{2.5}$ , CO,  $\text{SO}_2$ , and  $\text{NO}_2$ , but not ozone, were associated with hospitalization or mortality from stroke (Shah et al. 2015). A 10  $\mu\text{g}/\text{m}^3$  increase

in PM<sub>10</sub> or PM<sub>2.5</sub> was associated with a RR of 1.011 (95 % CI 1.011–1.012) and 1.003 (95 % CI 1.002–1.004), respectively. Authors reported stronger associations for NO<sub>2</sub> and PM<sub>10</sub> in studies from low or middle income countries. Results consistent with these were reported in another meta-analysis focusing on PM pollution (Wang et al. 2014).

Studies of long-term exposure and stroke have been summarized in several reviews (Faustini et al. 2014; Ljungman and Mittleman 2014; Hoek et al. 2013; Lee et al. 2018). In general, positive associations have been reported for PM and NO<sub>2</sub> in relation to both hospitalization and mortality from stroke although fewer studies have considered gaseous pollutants. The Women's Health Initiative reported a 28 % increased risk of stroke incidence per 10 µg/m<sup>3</sup> PM<sub>2.5</sub> (HR 1.28 95 % CI 1.02–1.61) (Miller et al. 2007). In the ESCAPE project from 11 European cohorts, a 5 µg/m<sup>3</sup> increase in annual PM<sub>2.5</sub> was associated with a non-significant 19 % higher risk of incident stroke (HR 1.19, 95 % CI 0.88–1.62) with similar findings for PM<sub>10</sub> (Stafoggia et al. 2014). Stronger associations were observed in elderly and in those exposed living in low-exposure areas (HR 1.33, 95 % CI 1.01–1.77 in area with <25 µg/m<sup>3</sup> annual mean).

There is strong support for positive associations between short-term air pollution exposure and stroke and moderately strong evidence for long-term exposure. Some of the studies point to more consistent evidence for ischemic stroke although this varies regionally with higher incidence rates for haemorrhagic stroke in e.g. East Asia.

### Arrhythmias

Changes in the variability of time between normally conducted heart beats, so called heart rate variability (HRV), can be calculated in a number of ways and have been used to characterize the parasympathetic and sympathetic heart tone. Reductions in these measures, meaning a more monotonic heart rate, has been associated with higher cardiovascular morbidity and mortality (Sassi et al. 2015; Heart rate variability 1996; Arora 2012). In a meta-analysis of 29 studies including a total of 18,667 participants, a 10 µg/m<sup>3</sup> increase in short-term PM<sub>2.5</sub> exposure on the order of hours, up to 24 hours, was associated with between 0.12–2.44 % lower indexes of HRV (Pieters et al. 2012), implying autonomic dysfunction in association with air pollution exposure.

Short-term exposure to ultra-fine particles, fine particles and NO<sub>2</sub> has also been associated with supraventricular and ventricular runs of tachycardia in men with CHD (Berger et al. 2006). In the Womens' Health Initiative including 57,422 women, PM<sub>2.5</sub> and PM<sub>10</sub> were strongly associated with ventricular ectopy in smokers (OR 2.0, 95 % CI 1.32–3.3; and 1.32, 95 % CI 1.07–1.65 per 10 µg/m<sup>3</sup> pollutant respectively) but not in non-smokers and no associations were found for supraventricular ectopy (Liao et al. 2009). Fine particles have also been associated with electrocardiogram (ECG) changes such as P-wave complexity and PR duration, considered harbingers of AF (Liao et al. 2010). AF is the commonest form of arrhythmia and a major risk factor for stroke and may many times be asymptomatic or with few or unspecific symptoms, making it challenging to study using conventional methods such as hospital admissions databases. In fact, a large case-crossover study of 10,000 hospital admissions did not observe associations with air pollution but by definition only considered AF with symptoms necessitating hospital admission and may have been affected by difficulties in assessing time of symptom debut (Bunch et al. 2011). In contrast, a 6 µg/m<sup>3</sup> increase of the 2-hour average



PM<sub>2.5</sub> was associated with a 26 % higher risk of AF (95 % CI 8–47 %) in patients with implantable cardioverter defibrillators (ICD) (Link et al. 2013). These patients have ICDs due to a high risk of ventricular arrhythmias and consequently have detailed continuous intra-cardiac ECG monitoring able to record time and type of arrhythmia episode.

Short-term air pollution exposure has also been investigated in relation to cardiac arrest and ventricular arrhythmias that are frequently the immediate cause of cardiac arrest. Fifteen studies have been conducted investigating air pollution and cardiac arrest including cities such as Beijing (Xia et al. 2017), Seoul (Kang et al. 2016), Okayama (Yorifuji et al. 2014), Perth (Straney et al. 2013), Melbourne (Dennekamp et al. 2010), New York City, Houston (Ensor et al. 2013), Seattle (Levy et al. 2002; Sullivan et al. 2003), Indianapolis (Rosenthal et al. 2008), Bordeaux (Pradeau et al. 2015), Rome (Forastiere et al. 2005), Copenhagen (Wichmann et al. 2013), Helsinki (Rosenthal et al. 2013), and Stockholm (Raza et al. 2014), overwhelmingly focusing on PM<sub>2.5</sub>. Positive associations were reported from most studies in order of 1–12 % higher risk per 10 µg/m<sup>3</sup>. Associations with NO<sub>2</sub> and ozone were also reported in some of the studies including in Sweden (Xia et al. 2017; Kang et al. 2016; Yorifuji et al. 2014; Ensor et al. 2013; Pradeau et al. 2015; Rosenthal et al. 2013; Raza et al. 2014).

Air pollution associations with ventricular arrhythmias have been studied in patients with ICDs and several including in Sweden have demonstrated positive associations with higher PM, NO<sub>2</sub> or SO<sub>2</sub> exposure, even within a few hours (Ljungman et al. 2008; Rich et al. 2006 and 2005; Dockery et al. 2005; Metzger et al. 2007). Other studies with a lower time resolution of exposure did not support associations between air pollutants and ventricular arrhythmias (Rich et al. 2004; Vedal et al. 2004).

A review of acute controlled air pollution exposure studies of human subjects concluded that air pollution did not increase the risk of arrhythmias (Langrish et al. 2014). These studies leverage the methodological strength of experimental settings including double-blind randomized crossover exposure and include both healthy individuals and patients with stable CHD. However, they are limited to studying air pollution increases within very short time frames.

There is a considerable paucity of studies considering long-term exposure to air pollution and arrhythmias, however some studies are worth mentioning. In a Swiss cohort of 1,607 participants undergoing 24-hour ECG monitoring, a 1 µg/m<sup>3</sup> increase in the 10-year average PM<sub>10</sub> was associated with a 14.5 % lower high frequency power HRV (95 % CI -25.9– -1.3 %) in participants with angiotensin converting enzyme (ACE) inhibitor therapy (Felber et al. 2008). In the same cohort NO<sub>2</sub> was associated with reduced HRV in women, elderly and subjects with heart disease (Adam et al. 2012). The Multi-Ethnic Study of Atherosclerosis (MESA) including 4,783 participants from 6 US cities reported associations between long-term PM<sub>2.5</sub> exposure and prevalent QT prolongation (heart rate adjusted QT duration >95<sup>th</sup> centile of race-specific cutoffs) (OR 1.6, 95 % CI 1.2–2.2 per 10 µg/m<sup>3</sup>) and intraventricular conduction delay (QRS duration >120ms) (OR 1.7, 95 % CI 1.0–2.6) (Van Hee et al. 2011). These ECG parameters have been associated with higher risk of ventricular arrhythmias and cardiovascular mortality (Elhendy et al. 2005; Kashani and Barold 2005; Newby et al. 1996; Lee et al. 2003).

The evidence from epidemiological studies suggests that both short-term and long-term exposure to air pollution may exert effects on the electrical conduction system of the heart. In

some cases, exposure may lead to clinically relevant arrhythmic disease such as cardiac arrest or AF, however, very little research has been conducted using long-term exposure and there remains a fair degree of uncertainty regarding AF.

## Subclinical disease

### Vascular effects

Studies have investigated the role of air pollution exposure in development of vascular dysfunction, atherosclerosis and cardiac remodeling, precursors of clinical outcomes. Indicative are findings from a study using a mouse model exposed to long-term exposure to PM demonstrating accelerated atherosclerosis, increased vasoconstrictive responsiveness and vascular inflammation (Sun et al. 2005). A multitude of studies from animal models have likewise demonstrated accumulation of foam cells in atherosclerotic plaque (Cao et al. 2016). Supporting this experimental research, observational studies have reported associations between long-term exposure to traffic-pollutants and increased carotid intima media thickness and coronary calcium score (Kunzli et al. 2005 and 2010; Hoffmann et al. 2007; Kaufman et al. 2016; Wilker et al. 2013; Rivera et al. 2013). The MESA used a repeated measures design of carotid ultra-sound examinations to demonstrate associations between higher long-term PM<sub>2.5</sub> exposure and greater progression in CIMT and in addition observed slower progression in regions with reductions in PM<sub>2.5</sub> over time (Adar et al. 2013). MESA and the Framingham Heart Study cohorts also demonstrated that long-term and short-term exposures affect both chronic vascular endothelial function and disturbances in peripheral microvasculature in the retinal arterioli and digital circulation (Wilker et al. 2014; Ljungman et al. 2014; Krishnan et al. 2012; Adar et al. 2010). Some of these vascular responses may in the case of diesel exhaust be due to a reduced NO bioavailability as a consequence of increased consumption within the vasculature owing to systemic oxidative stress (Langrish et al. 2013; Wauters et al. 2013). In addition to atherosclerotic effects and changes in vascular function, short-term increases in both diesel and coarse particles have been demonstrated to lead to increases in blood pressure in experimental controlled human exposure studies (Cosselman et al. 2012; Brook et al. 2014), and long-term exposure to air pollution has also been associated with increased prevalence and incidence in hypertension in large cohorts in both low and high pollution level settings in Los Angeles, Europe and Ontario, Canada (Coogan et al. 2012; Chen et al. 2014; Fuks et al. 2014).

### Cardiometabolic effects

Recent work has also highlighted a possible link between air pollution exposure and metabolic effects such as development of insulin resistance and diabetes, significant risk factors for CVD. In children from two German birth cohorts, long-term exposure to traffic-related pollution (NO<sub>2</sub> and PM<sub>10</sub>) was associated with higher insulin resistance (Thiering et al. 2013) and in a large study including 62,012 individuals living in Ontario, Canada, diabetes incidence increased by 11 % per 10µg/m<sup>3</sup> in 6-year averaged PM<sub>2.5</sub> levels at the residential postal code (Chen et al. 2013). Furthermore, long-term PM<sub>10</sub> pollution was also associated with reduced metabolic control (measured by HbA1c) in 9,102 newly diagnosed type 2 diabetes (T2DM) patients across Germany (Tamayo et al. 2014). This emerging evidence provides further evidence for other pathways in which air pollution exposure may lead to CVD.

## Mechanisms

Air pollution has been proposed to contribute to cardiovascular morbidity and mortality through several different mechanisms leading to subclinical pathogenesis and ultimately to overt CVD.

### Inflammation, oxidative stress and pro-thrombosis

Toxicological studies in animal models and cell cultures as well as controlled human exposure studies have in a wealth of studies indicated that exposure to particulate matter, NO<sub>2</sub>, and ozone increases pulmonary and systemic inflammation and oxidative stress as well as contributing to a pro-thrombotic state (Brook et al. 2010 and 2004; US-EPA 2016 and 2013; Lucking et al. 2011). Some of the effects by PM have been suggested to be exerted locally after translocation of particles across the blood-alveolar barrier, however, initial studies to support particle translocation have not been confirmed in latter work despite efforts (Mills et al. 2006). Relative to PM and ozone, the experimental evidence for extra-pulmonary effects of NO<sub>2</sub> are relatively less well-established. While carbon monoxide is known to cause hypoxemia and thus ischemia-related health outcomes it is unclear whether this occurs to significant degree at ambient exposure levels. However, toxicological studies have suggested that carbon monoxide at environmentally occurring levels may initiate adverse pathways via cellular signaling leading to inflammatory and oxidative stress upregulation (US-EPA 2010). There is very little evidence in toxicological and controlled human exposure studies to suggest changes in inflammatory status, increased oxidative stress or pro-thrombosis from SO<sub>2</sub> exposure (US-EPA 2008).

### Autonomic imbalance

In addition to the above-mentioned changes in cellular and humoral immune responses, the biological initiation of health effects of air pollution has also been proposed to act via a direct activation of pulmonary neural reflex arcs affecting the autonomic nervous system. Toxicological and controlled human exposure studies of both PM and ozone lend support to this pathway of effect (Brooks et al. 2004 and 2010; US-EPA 2013). Evidence does not, however, support these effects following ambient NO<sub>2</sub>, CO, or SO<sub>2</sub> exposure (US-EPA 2008, 2010 and 2016).

### Epigenetics

Some of the effects of especially PM exposure have been proposed to be exerted through epigenetic changes. PM exposure has been associated with DNA methylation in observational studies (Baccarelli et al. 2009; Madrigano et al. 2011), and controlled human exposure to PM<sub>2.5</sub> has demonstrated changes in blood pressure related to lower DNA methylation in circulating leukocytes (Bellavia et al. 2013). Diesel particle exposure in pregnant mice was associated with myocardial fibrosis and susceptibility to heart failure in offspring raised with filtered air exposure to adulthood (Weldy et al. 2013 and 2014). Results were interpreted as mediated through epigenetic changes although epigenetic effects were not directly examined.

Possible transgenerational effects of exposure may potentially present important public health consequences.

## Conclusions

In summary, air pollution is a collective name for a number of different individual pollutants including gaseous compounds and a multitude of particle matter pollutants. Air pollution contains various mixtures of these individual pollutants that emanate from multiple sources with different temporal and spatial distributions and most likely different toxicities. Although considerable research has been conducted to disentangle which air pollutants cause which health effects, it remains difficult to single out any specific pollutant. That being said, the vast majority of the evidence indicates strongest associations to be found between fine PM and CVD. Health effects can be identified both after short and long-term exposure to air pollution. There is especially strong evidence for short-term exposure to PM and cardiovascular mortality, IHD incidence, heart failure and stroke as well as between long-term exposure and cardiovascular mortality and IHD incidence. Although there is some evidence to suggest associations between air pollution exposure and arrhythmias, results reveal some inconsistencies and long-term studies and studies of AF are lacking. On a whole, air pollution accounts for a considerable proportion of the global burden of disease accounting for 1 out of 9 deaths globally. While levels of e.g. PM pollution have shown leveling off or reductions in high income countries as a result of regulation, levels are increasing at an alarming rate in middle and low income countries posing a considerable challenge to global cardiovascular health.

## Research needs

- More studies of short- and long-term exposure to air pollution in relation to risk of AF are needed.
- Air pollution is a changing mix of components and sources and efforts are warranted that can elucidate the most important sources and components as well as determine interactions between components can have policy relevant implications.
- Most research in air pollution epidemiology has been conducted in low- or middle-exposure settings in Europe and North America from whence our current understanding of exposure-response relationship is derived. However, the majority of the globe's population is to an increasing degree exposed to high-level air pollution. Efforts to explore exposure-response functions are therefore warranted for high-exposure environments in lower and middle income countries. Indeed, these populations may include additionally vulnerable subgroups due to nutritional deficiencies, anemias caused by parasitic infections and socio-economic factors that need to be explored.
- To further increase our knowledge about air pollution in relation to risk of CVD, it seems relevant to explore interactions between air pollution and other common environmental exposures in the urban environments including noise, green space, heat islands, and physical activity.

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## 6. Urban greenness

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### Introduction

Cities are engines of innovation and wealth, and offer plentiful opportunities for public health improvement. At the same time, urban environments are often associated with environmental and behavioural health hazards such, as the increased exposure to noise and air pollution (Paciência and Moreira 2017; Nieuwenhuijsen 2018; Schultz et al. 2012; Lee et al. 2013; Willers et al. 2013; Cesaroni et al. 2014; Raza e al. 2014; Korek et al. 2015; Liu et al. 2009; Eriksson et al. 2007, 2010 and 2014; Bluhm and Eriksson 2011; Pyko et al. 2015 and 2017). Furthermore, modern urban landscapes, which have developed around car-use, often ignore other forms of transportation, such as walking and bicycling, and may thus encourage sedentary behaviour, leading to increased obesity, high blood pressure, and high rates of cardiovascular morbidity and mortality among citizens (Paciência and Moreira 2017; Nieuwenhuijsen 2018). Increasing populations' exposure to urban greenness has been suggested as a possible measure that can help to address these health problems in a preventive way (WHO 2016).

The causal relationship between exposure to natural environments and urban public health, has been a rapidly emerging field in environmental epidemiology during the past decade (Markevych et al. 2017). Consequently, a wealth of evidence now exists to suggest that even short-term exposure to natural settings can have a range of positive outcomes for health and wellbeing (WHO 2016; Bratman et al. 2012; Capaldi et al. 2014; Gascon et al. 2015; Hartig et al. 2014; Keniger et al. 2013; McMahan and Estes 2015; Sandifer et al. 2015). Many international studies, including a report from the WHO (2016), suggest that increased exposure to urban greenness is, for instance, associated with reduced general mortality, improved mental health, increased physical activity and better birth outcomes (WHO 2016; Fong et al. 2018; Kondo et al. 2018). Not all studies, however, find beneficial associations between greenness exposure and the health outcomes of interest and occasionally even negative associations are reported (e.g. Cummins and Fagg 2012; Flouri et al. 2014; Mowafi et al. 2012; Pereira et al. 2012; Potestio et al. 2009; Prince et al. 2011; Richardson et al. 2012).

Although many theories exist, greenness is generally thought to affect health by mitigating exposures to heat, noise and air pollution, relieving mental and physiological stress and promoting activities such as exercise and socializing (Markevych et al. 2017; Fong et al. 2018). Since all of these factors significantly affect cardiovascular health, it is biologically plausible to expect greenness exposure also to be associated with the cardiovascular health outcomes. This chapter aims to give an overview over the possible biological mechanisms linking cardiovascular health to exposure of urban greenness, and to briefly review the epidemiological studies that have investigated this relationship.

### Green structure, green infrastructure, green space, greenness or urban green?

Studies exploring the urban vegetation-public health relationship may use different terms/synonyms to define the population exposure to urban vegetation. Currently, there is no

universally accepted definition for any of these terms (e.g. ‘green space’, ‘green structure’, ‘urban green’, ‘greenness’ etc.). Thus, all of these may be used to refer either to an area with ‘natural surface’ or ‘natural settings’ in proximity to urban settings, or to some specific elements of nature in a built area, such as street trees, bushes, and ornamental plants. ‘Blue structure’ or ‘blue space’, representing water elements from ponds to coastal zones may be included in the urban greenness estimates in some studies, but not in others (WHO 2016). In the present chapter, we mainly use the term “urban greenness”, which here includes all vegetation and water bodies in urban settings.

Epidemiological studies generally use two types of indicators to estimate population exposure to greenness: proximity indicators and cumulative indicators (Ekkel and de Vries 2017). Proximity indicators, most commonly, refer to the geographical distance between the residential address of a study subject and a green area. However, the definition of ‘green area’ again differs between studies and rather depends on the local climatic/geographic and cultural factors. Proximity measurements may also vary depending on if they simply express a straight, linear distance between, for example, a home and a park; or if they estimate the path-length a person actually has to pass to reach a green area, taking into account the constraints in form of road network and structural barriers (walls, large roads, rivers) hindering the movement in a straight line. Epidemiological evidence today (mostly based on studies using a straight linear distance measure), suggest that 100–300m is a threshold distance between the place of residence and a green area, after which the use of a green area rapidly declines (Ekkel and de Vries 2017).

Cumulative indicators are used to quantify the amount of greenness within a certain area or neighbourhood, and usually constitute estimations of either the ‘percentage of green space’ or the average Normalized Difference Vegetation Index (NDVI) within the area of interest. Percentage of green space is most commonly estimated from land-use/land-cover maps or from photographic area images. The NDVI, however, is an indicator based on land surface reflection of visible red and near-infrared parts of the spectrum (reflecting the biomass of photosynthesising plants), and is derived from satellite images. The value of NDVI ranges between -1 and +1, with higher values indicating more greenness. One advantage with using NDVI over land-use maps is that even small natural elements, such as ornamental plants that may not be visible on land-use maps, are included and contribute to the exposure estimate (Ekkel and de Vries 2017).

In population-based studies, the quantity of greenness is typically estimated for circular areas surrounding a study subject’s place of residence. The buffer sizes for these circular areas vary (ranging from 50m to up to several kilometres) depending on the study. Browning and Lee (2017) reviewed articles that used such buffer analyses to identify trends between physical health and distance within which greenness is measured, and concluded that larger buffer sizes, up to 2000 m, better predicted physical health than smaller ones. However, it is possible that the optimal buffer size differs depending on the outcome, study population and geographic location in focus. According to a review by Ekkel and de Vries (2017), studies using cumulative greenness indicators are more consistently positively related to health than residential proximity ones.

## Potential pathways linking urban greenness and cardiovascular health

### Relaxation and restoration

Green and blue environments are suggested to have a relaxing effect, allowing people to recover from demanding situations (WHO 2016). It is plausible that urban greenness affects the brain and body via psycho-endocrine mechanisms, including the function of the hypothalamic pituitary adrenal (HPA) axis. The HPA axis regulates stress hormone, cortisol, secretion, and its dysregulation is associated with a wide range of disease outcomes and immune system malfunction (Tsigos and Chrousos 2002). Several studies have provided evidence for the potential role of urban greenness in buffering or reducing stress (Gidlow et al. 2016a; Park et al. 2010; Ward Thompson et al. 2012; Aspinall et al. 2015; Bratman et al. 2015; Van den Berg et al. 2010; Stigsdotter et al. 2010; Nutsford et al. 2016), however, the complexity and sensitivity of the stress regulation physiology (especially the manipulation and measurements of serum or salivary cortisol levels) is often a methodological complication. In a recent study by Egorov et al. (2017), allostatic load – a multiple biomarker-based measure of physiological dysregulation – instead of cortisol levels, was used as an estimate of chronic stress. The authors found that increased greenness around residential address reduced the allostatic load by about 37 %.

Several studies link occupational and life stress to increased rates of CHD and stroke, as well as to other cardiovascular conditions, such as AF (Kivimäki et al. 2015; Kivimäki and Kawachi 2015; Kivimäki and Steptoe 2018; Fransson et al. 2018; Huang et al. 2015; Orth-Gomér et al. 2000; Lee et al. 2003; Carey et al. 2014; Kario et al. 2003). Although the risk of CVD associated with stress in adulthood is usually lower than the risks associated with, for example, smoking, high blood pressure, or severe stressful experiences in childhood, adult stress may still be an important disease trigger in individuals with high atherosclerotic plaque burden and in those with pre-existing cardiovascular or cerebrovascular dysfunction (Kivimäki and Steptoe 2018). Since exposure to urban greenness is thought to evoke positive emotions, block negative thoughts and thereby ameliorate stress response, it may also constitute a pathway contributing to improved cardiovascular health.

### Improved social capital

Social relationships have a well-known protective health effect (Nieminen et al. 2010; Castro and Zautra 2016). Social isolation on the other hand is a predictor of morbidity and mortality (Pantell et al. 2013; Yang et al. 2016; Steptoe and Kivimäki 2012), and has been observed to increase, among others, the risk of hypertension, acute MI and stroke (Hakulinen et al. 2018; Xia and Li 2018). Increasing the quantity and quality of urban greenness is suggested to foster social interactions and promote a sense of community, among adults and children (de Vries et al. 2013; Seeland et al. 2009; Orban et al. 2017; Ruijsbroek et al. 2017), whereas a shortage of greenness in the residential environment is associated with feeling lonely and lacking social support (Maas et al. 2009; Ward et al. 2016).

### Improved functioning of the immune system

Enhanced immune functioning has been suggested to be a central pathway between nature and health (Kuo 2015). Evidence supporting this hypothesis is, however, sparse and mainly based on publications that are, for example, reporting the immune system stimulating effects of Japanese “forest bathing” tradition (Li 2010); as well as on studies indicating that increased exposure to biodiversity, natural allergens and diverse microorganisms in natural environments is associated with beneficial health outcomes (Rook 2013; Lynch et al. 2014).

However, another possible mechanism, through the previously described pathway of relaxation/stress reduction, could be relevant in linking nature exposure to improved immune function. It is well-known that chronic stress suppresses and dysregulates both innate and adaptive immune response (Dhabhar 2014). Among other effects, chronic stress alters Type 1-Type 2 cytokine balance, causes B-cell decrements, induces low-grade chronic inflammation, and suppresses the quantity, movement and function of several types of immune-protective cells (Dhabhar 2014; McGregor et al. 2016). Consequently, through its immune-modulating effects chronic stress is likely to increase susceptibility to a large number of diseases (Steptoe and Kivimäki 2012). By buffering the negative effects of stress, greenness may thus promote immune function and contribute to, among others, better cardiovascular health. In Egorov et al. (2017) the risk of having high levels of certain inflammation markers in blood serum, previously associated with high chronic stress, was reduced by increased amount of residential greenness.

### Enhanced physical activity, improved fitness and reduced obesity

Physical activity has a well-established positive impact on health and on cardiovascular function in particular (WHO 2016; Barengo et al. 2017; Lachman et al. 2018). According to Lear et al. (2017), both recreational and non-recreational physical activity can decrease the risk of CVD events (e.g. incidents of MI, stroke, and heart failure) and mortality regardless if the population in focus is from a low-, middle-, or high-income country.

Abundant vegetation and bodies of water may provide an inviting setting for physical activity, and accordingly, studies from all over the world have reported that recreational walking, increased physical activity and reduced sedentary time are associated with the use of and access to urban green areas (Fong et al. 2018; Veitch et al. 2016; Christian et al. 2017; Dadvand et al. 2014; Wendel-Vos et al. 2004; Kaczynski and Henderson 2007; Astell-Burt et al. 2013; Sugiyama et al. 2015; Akpinar 2016; Pietilä et al. 2015), particularly among certain groups, such as dog owners (White et al. 2018). A recent systematic review by Fong et al. (2018) further confirmed the strong link between greenness and physical activity (both self-reported and objective); however, the authors also stress the potential for self-selection in previous literature, implying that individuals with healthier behaviours may choose greener areas to live in. Studies that have not concentrated on physical activity as the main health outcome, but have used mediation analysis to investigate whether physical activity constitutes a causal pathway between green structure and some other health outcome (e.g. depression, self-reported general health) have yielded mixed findings (de Vries et al. 2013; McEachan et al. 2016; Richardson et al. 2013; Sugiyama et al. 2008; Dadvand et al. 2016; Maas et al. 2008; Triguero-Mas et al. 2015), suggesting that other pathways than physical activity may be more important in certain settings.

### Anthropogenic noise buffering

Growing international evidence indicates that exposure to traffic noise (including motor vehicle, railway and air traffic noise), is associated with serious health effects including increased risk for various cardiovascular and metabolic diseases (Eriksson et al. 2007, 2010 and 2014; Bluhm and Eriksson 2011; Pyko et al. 2015 and 2017). Since noise has been associated with a multitude of the same health outcomes as green structure, it is likely that noise also lies on the causal pathway between urban green structure and health (Markevych et al. 2017). Almost all proposed mechanisms whereby noise exposure may affect health base on the assumption that noise is primarily a psychological stressor (Recio et al. 2016). Thus, supported by the above-mentioned evidence for the stress-buffering properties of urban green and blue structure, it is likely that urban nature, in some degree, ameliorates the negative health effects triggered by noise.

A handful of studies have demonstrated significantly reduced noise annoyance in people living in greener neighbourhoods (Gidlöf-Gunnarsson et al. 2007 and 2009; Li et al. 2010 and 2012; Leung et al. 2014; Bodin et al. 2015; Van Renterghem and Botteldooren 2016). Strategically placed green structure in form of green barriers, green facades and green roofs has also been considered as a means to reduce outdoor noise exposure acoustically (e.g. Van Renterghem et al. 2015; Martinez-Sala et al. 2006), and appears to reduce noise levels by 5–10 dB, either through diffraction, absorption or destructive interference of sound waves (Van Renterghem et al. 2015). It is however important to remember, that abundant vegetation in an urban area generally automatically leads to lower noise levels, simply due to the lack of, or reduction in the space available for noise-emitting sources (Markevych et al. 2017).

### Reduced exposure to air pollution

Air pollution is an important public health concern, increasing mortality, and affecting respiratory, cardiovascular and metabolic health (Schultz et al. 2012; Lee et al. 2013; Willers et al. 2013; Cesaroni et al. 2014; Raza et al. 2014; Korek et al. 2015; Liu et al. 2009; Panasevich et al. 2009; Shaposhnikov et al. 2014). As is the case of noise, the quantity of primary sources of air pollution is generally low in green urban areas, automatically leading to lower concentrations of air pollutants. Urban vegetation, especially trees, have been suggested to be able to improve air quality by removing pollutants (Nowak et al. 2006; Jim and Chen 2008; Selmi et al. 2016); however, the efficiency of this process at different locations and by different species is still unclear (Vos et al. 2013). In epidemiological models, exploring the greenness-health relationship, air pollutants are, as a rule, included as potential confounders (Markevych et al. 2017), although only one study has shown evidence of this effect (Thiering et al. 2016). A couple of investigations that have used mediation analyses to test whether air pollution acts as a mediator in the link between green structure and health outcomes, have found support for partial mediation (James et al. 2016; Dadvand et al. 2015).

### Reduction of the urban heat island effect

Studies from Central Europe have indicated that heat-related public mortality (including cardiovascular mortality) is significantly higher in densely populated urban centres than in their



more sparsely-populated surroundings (Wolf et al. 2015). The reason for this is that the infrastructure in areas of high population density is typically constructed of materials (concrete, asphalt etc.) with increased capacity to absorb, maintain and re-radiate solar radiations, leading to locally increased temperatures, especially during night-time. This phenomenon is known as the "urban heat island" effect. The severity of the urban heat island effect depends on the size of the city and on the population density (Oke 1973).

Numerous studies have investigated and provided evidence for the cooling effects of urban green and blue environments (e.g. Völker et al. 2013; Shishegar 2014; Jenerette et al. 2011; Bowler et al. 2010). Burkart et al. (2016) linked the cooling effect of urban greenness to public mortality data and reported a mitigating effect of both the quantity of urban green structure and of the closeness to bodies of water on heat-related mortality in the elderly population of Lisbon. Abundant greenness in built areas may thus be an important factor reducing the risk for, among other health outcomes, cardiovascular mortality during heatwaves.

#### Optimised exposure to sunlight and improved sleep

If access to green and blue structure is associated with more time spent outdoors, it is also likely to be accompanied by increased exposure to sunlight. Exposure to sunlight is crucial for human D-vitamin production, and optimum levels of vitamin D are important for a multitude of physiological functions contributing to health and well-being. Increasing the time spent on outdoor activities significantly decreases the risk for vitamin D-deficiency (Cherrie et al. 2015; De Rui et al. 2014). Further, exposure to ultraviolet (UV) light, has often been associated with negative health effects; however, a recent study has indicated that UV-induced release of NO in the skin might contribute to better health by lowering the risk of hypertension and CVD (Liu et al. 2014). Exposure to daylight, in general, stimulates alertness, controls circadian rhythms and promotes healthy sleep. Adequate sleep is crucial for good health, and sleep deprivation has been linked to many adverse health effects (Leproult et al. 1997; Frey et al. 2007; Mullington et al. 2009). Several studies suggest that living in a greener neighbourhood lowers the risk for insufficient sleep (WHO 2016; Astell-Burt et al. 2013; Grigsby-Toussaint et al. 2015). It is possible that increased greenness increases people's exposure to natural daylight and in this way helps to maintain circadian rhythms.

#### Urban greenness and cardiovascular health

Both experimental and population-based approaches have been used to study associations between greenness exposure and CVD risk. In experimental studies, typically, an objective measurement of various estimates of cardiovascular health (blood pressure, heart rate etc.) is conducted. In population/register based studies, the definition of 'cardiovascular' health outcomes most often includes all circulatory system diseases (i.e. ICD-10, codes I00–I99) ranging from 'hypertensive diseases' to 'cerebrovascular' health outcomes. Occasionally, however, cerebrovascular outcomes (codes I60–I69) or stroke are reported separately. Population studies are generally in higher degree than experimental studies adjusted for other possible environmental exposures, such as air pollution and (more seldom) noise and temperature.

### Experimental studies linking urban greenness to cardiovascular health

Experimental studies, focusing on short-term effects of greenness exposure on cardiovascular function, use either between- or within-subject designs (e.g. Hartig et al. 1991; South et al. 2015; Brown et al. 2014; Grazuleviciene et al. 2016; Lanki et al. 2017; Gidlow et al. 2016b; Song et al. 2013, 2014 and 2015). Typically, in these studies the subjects are asked to walk in either natural or built environments for a certain period of time. The predominant health outcomes in these field experiments include measurements of heart rate and HRV, and occasionally, blood pressure.

When the within-subject design is used, generally, participants walk for a set amount of time (e.g. 15–30 minutes) in an urban green area, and then the same amount of time in a built space (Lanki et al. 2017; Gidlow et al. 2016; Song et al. 2013, 2014 and 2015). Studies using the between-subjects design, usually randomly divide participants into different environmental exposure groups (e.g. built street, urban park, indoor seating etc.) and measure physiological responses to a repeated exposure, e.g. daily 30-minute walks for seven days (Grazuleviciene et al. 2016), or two 20-minute walks/week for eight weeks (Brown et al. 2014).

With a few exceptions (Hartig et al. 1991; Brown et al. 2014), experiments measuring heart rate response, have found evidence for lower heart rate in people exposed to urban green environments compared to the exposure to control conditions (e.g. built or indoor conditions) (South et al. 2015; Grazuleviciene et al. 2016; Lanki et al. 2017; Song et al. 2013, 2014 and 2015). The measurements of HRV, however, have been methodologically inconsistent and the findings mixed (Brown et al. 2014; Lanki et al. 2017; Gidlow et al. 2016b; Song et al. 2013, 2014 and 2015). Lower blood pressure in participants visiting a green area has been reported in a couple (Lanki et al. 2017; Tamosiunas et al. 2014), but not in all studies measuring this outcome (Hartig et al. 1991). However, it is interesting to mention here that three studies examining the associations between short-term exposure to *simulated* green space and blood pressure, found a small reduction in blood pressure in subjects that viewed videos of green space compared to those viewing urban landscapes (Pretty et al. 2005; Duncan et al. 2014a and 2014b). In general, the experimental studies regarding cardiovascular health outcomes have been based on small sample sizes and have not controlled for confounding factors (Kondo et al. 2018), with an exception of Lanki et al. (2017) who demonstrated that including particulate air pollution and noise in the models slightly weakened the associations between environmental exposure and indicators of cardiovascular health.

### Population studies

Population studies, exploring the urban greenness-cardiovascular health relationship, published before 2015, are dominated by cross-sectional and ecological study designs. Recent publications have increased the amount of prospective studies, still, more of these, with multiple cardiovascular endpoints are needed to add clarity to this exposure-outcome relationship (Fong et al. 2018). The strength of evidence from studies linking greenness to improved cardiovascular health is presently estimated to be intermediate (Fong et al. 2018; Kondo et al. 2018; Gascon et al. 2016; James et al. 2015).

### *Cardiovascular mortality and urban greenness*

Gascon et al. (2016), published a systematic review, including eight studies, published 2014 or earlier, exploring the relationship between cardiovascular mortality and greenness exposure. After conducting a meta-analysis, the authors found an overall small ( $\approx 5\%$ ) but significant reduction in the cardiovascular mortality associated with increased exposure to greenness. Six of the eight included studies, used ecological design, four of these reported that areas with more greenness had lower levels of stroke (Hu et al. 2008) and CVD mortality (Mitchell and Popham 2008; Richardson and Mitchell 2010), whereas two did not identify any significant relationships (Richardson et al. 2010 and 2012).

Two of the ecological studies included in the above-mentioned meta-analysis also explored the role of socioeconomic factors mediating the green structure effect. A UK-wide analysis by Mitchell and Popham (2008) investigated whether income-related health inequalities decreased in populations with greater exposure to urban greenness, and found that health inequalities related to income deprivation regarding mortality from circulatory diseases were indeed lowest in populations living in the greenest areas. Similarly, Lachowycz and Jones (2014) reported that the relationship between greenspace access and reduced cardiovascular mortality was only apparent in the most deprived areas in UK.

The above-mentioned review by Gascon et al. (2016), only identified two prospective cohort studies published before 2014 (Tamosiunas et al. 2014; Villeneuve et al. 2012). The first of them, a longitudinal study by Villeneuve et al. (2012) based on data from about 575,000 adults residing in urban areas in Ontario, Canada, reported that increased levels of residential greenness significantly reduced the risk for cardiovascular mortality, including the risk for mortality from IHD and stroke. The second study, by Tamosiunas et al. (2014) reported an increased risk for combined non-fatal and fatal CVD with increased distance between residential address and a green area in adults residing in Kaunas, Lithuania. A natural experiment from USA (not included in Gascon et al.) explored whether the loss of 100 million trees due to emerald ash borer (an invasive pest organism) influenced the levels of cause-specific human mortality in 15 affected USA states, and found evidence for significantly increased mortality due to cardiovascular illnesses in counties that were infested by the pest organism (Donovan et al. 2013).

Later studies associating green structure exposure to cardiovascular mortality have added more prospective analyses, most of them strengthening the evidence for a green structure-cardiovascular health relationship. Wilker et al. (2014) conducted a longitudinal analysis based on survival data from patients admitted to an USA hospital due to acute ischemic stroke, and found that residential proximity to green areas was associated with higher survival rates. A recent study from Switzerland, based on data from the Swiss National Cohort (SNC), including 4.2 million adults, demonstrated a protective effect of residential greenness regarding cardiovascular mortality, independent from other environmental exposures such as air pollution and noise (Vienneau et al. 2017). Increased residential greenness was also found to significantly decrease the mortality caused by combined circulatory system diseases, and by stroke (analysed separately) in community-dwelling elderly ( $\geq 65$  years at baseline) in Hong Kong, China. An American study, based on data from a nationwide women's cohort, on the other hand, did not find any effect of residential green structure on cardiovascular mortality (James et al. 2016).

Among the most recent literature are also a couple of ecological investigations. One of them, by Wu et al. (2018) used several spatial analysis techniques to explore the relationship between the occurrence of sudden cardiac deaths (SCD) and urban greenness in North Carolina, USA. They found that the incidence of SCDs was inversely associated with the percentage of forest in the area and with the density of green paths. Another study, conducted in Rio de Janeiro, Brazil, investigated the relationship between greenness exposure, IHD and cerebrovascular diseases. They found that in areas with the quantity measures of greenness above the third quartile, mortality due to IHD was reduced by 6.7 % and due to cerebrovascular disease by 4.7 %. Again, the results showed highest beneficial health effects in those with lower socioeconomic level (Silveira and Junger 2018).

#### *Morbidity and other endpoints associated to cardiovascular health in relation to urban greenness*

Results from the literature assessing the effect of urban greenness on other cardiovascular outcomes than mortality also present mixed evidence. As was the case with mortality studies, the articles published before 2015 on this topic are generally dominated by cross-sectional analyses, while the newer research has added several longitudinal studies.

Maas et al. (2009) used cross-sectional morbidity data, provided by general practitioners in the Netherlands, from more than 300,000 individuals and found that higher residential greenness was associated with lower odds for CHD, but not for stroke, brain haemorrhage, cardiac disease and blood pressure (Maas et al. 2009). In accordance to studies mentioned in the last paragraph, the health benefits of green structure were found to be greater among population groups with lower levels of education compared to higher levels. Pereira et al. 2012 associated higher variability of residential greenness, but not the absolute greenness, with lower odds for hospitalisation for heart disease and stroke in a cross-sectional study from Australia (Pereira et al. 2012). Rickardson et al. (2013) linked neighbourhood-level green space availability to CVD data in the respondents to the New Zealand Health Survey and reported that CVD risk was reduced in all neighbourhoods with increased green space availability. Authors' attempt to establish a dose-response relationship between disease risks and green structure availability, however, did not give any significant results. Based on the data from a large US cohort of women, the Women's Health Initiative, Donovan et al. (2015) investigated whether the loss of trees due to the emerald ash borer affected the risk estimates for CVD, and reported a 41 % increase in risk of CVD in populations living in infested counties compared to non-infested ones. Lastly, a prospective analysis from south Israel, based on 23,110 subjects, all of them presenting at least one cardiovascular risk factor, associated higher levels of residential greenness to lower odds of MI, but not stroke (Yitshak-Sade et al. 2017). Since this study was conducted in an area with mainly desert terrain, it presented very low levels of greenness compared to most European studies; however, this study may confer some evidence for the importance of location-specific relative greenness levels (Fong et al. 2018).

Several studies have focused specifically on the relationship between blood pressure and green structure exposure. A cross-sectional analysis by Markevich et al. (2014) showed that both systolic and diastolic blood pressure were lower among children from a German birth cohort, who had higher residential greenness (Markevych et al. 2014). Associations between proximity to city parks and blood pressure during the first trimester of pregnancy were explored in women

residing in Kaunas, Lithuania, (Grazuleviciene et al. 2014) and also suggested a possible beneficial impact of nearby parks on the maintenance of normal blood pressure. A more long-term effect of urban greenness on blood pressure was studied in a recent report from Belgium (Bijnens et al. 2017). In this study, the ambulatory (24-h) blood pressures were obtained from 132 pairs of twins aged 18 to 25. The results showed that night-time systolic blood pressure was inversely associated with residential greenness in individuals living at the same address their entire life (an interquartile increase in residential greenness exposure was associated with on average 3.59 mmHg lower adult night systolic blood pressure). However, among twins, who were living at a different address than their birth address at time of the measurement, only residential greenness exposure in early-life was significantly associated with night systolic blood pressure. A longitudinal Australian study, by Paquet et al. (2014), however, did not find any associations between residential green structure and incidence of hypertension.

A longitudinal analysis, investigating associations between residential greenness and blood lipids that are risk factors for CVD (such as total cholesterol, high density lipoprotein [HDL], LDL and triglyceride) in 10–15-year-old individuals belonging to two German birth cohorts, did not find any associations (Markevych et al. 2016). Similarly, the Australian study by Paquet et al. 2014, could not associate residential greenness to incidences of dyslipidaemia. On the other hand, an investigation from Florida, USA, exploring the relationship between neighborhood greenness and occurrence of several chronic cardio-metabolic conditions (Brown et al. 2016) reported that increasing the neighbourhood greenness level from one standard deviation (SD) less to one SD more than the average value reduced the risk of diabetes by 14 %, hypertension by 13 %, and hyperlipidaemia by 10 %.

### Conclusions and future research needs

Although the number of good quality studies on greenness and CVD is growing and the majority of the evidence available today suggests that urban greenness has a beneficial effect on cardiovascular health, the findings are still inconsistent across studies. The strength and direction of the associations between green structure and cardiovascular health may also differ depending on several socio-demographic factors, such as, for example, education and income level, but also gender, age and ethnicity, which are not always taken into consideration. Further research including more comprehensive and multi-dimensional metrics is warranted.

From the city planning perspective, special effort should be made to increase green space in low-income neighborhoods, as these are likely to house the most vulnerable part of the population. While compensating for the lack of green structure by travel and summerhouses is an alternative for high-income takers, it is most likely not possible for low-income takers, which makes the low-income groups in higher degree dependable on the health benefits from the greenness close to their neighborhoods.

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## 7. Climate-related heatwaves

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### Introduction

Heat is a natural hazard, and its deleterious effects on the human body are widely recognized (Kovats and Hajat 2008). Despite the considerable human capacity to adapt to varied climates and environments, there are clear and absolute limits to the amount of heat exposure an individual can tolerate. Generally, the physiology, behaviour and culture of human populations is acclimatized to their local climate. Prolonged periods with higher than usual temperatures for a specific region, however, can have significant impacts on public health (Kovats and Hajat 2008).

After the shocking number of excess deaths observed in several European countries during the 2003 heat wave (Robine et al. 2008), the interest in preventing heat-related ill health increased significantly not only in Europe, but worldwide. Thus, since 2003, considerable research effort has been conducted to estimate the impact of the temperature-related mortality and morbidity, the geographical differences in the impact, and the specific individual social and clinical factors that increase vulnerability to heat (Staffoggia et al. 2008). As a result, most countries in Western Europe have today implemented some kind of heat-health warning systems and the cooperation between countries on the topic has increased significantly (Bissolli et al. 2016).

High ambient temperatures induce substantial physiological stress (Kenney et al. 2014). In hot environments, humans increase the blood flow in the skin, and the sweat rate. These processes are adaptive, but place a great demand on the cardiovascular system by necessitating a marked increase in cardiac output (Kenney et al. 2014). Consequently, a large fraction of the observed excess morbidity and mortality during heat waves is not directly heat-related, but rather attributable to increased physiological challenges, associated with thermoregulatory responses to heat. Elderly individuals especially, even in the absence of overt chronic disease, are sensitive to heat (Kenney et al. 2014).

Determinants of heat wave-related mortality are, however, not all physiological. Vulnerability to heatwaves varies on a regional level due to different climatic conditions, population characteristics and local adaptation measures. Individual heat vulnerability depends on a combination of both person-specific (age, gender, income, ethnicity) and contextual (population density, urban characteristics, socio-economy, access to health services) factors, and may differ not only between countries or municipalities, but also between closely situated neighborhoods in the same city (Åström 2017; de' Donato et al. 2015). A homebound lifestyle and lack of contact with other people has been shown to further increase the vulnerability, and in similarity to other health risks, heat stress is more likely to affect residents at the lower end of the socio-economic spectrum (Quinn et al. 2014). In addition, episodes of unusually high temperature (heatwaves) are often associated with other health hazards, such as increased production of ground-level ozone, wild fires, and water or electrical supply failures, which increase the negative implications for public health (Kovats et al. 2008).

## Thermoregulation – a challenge for cardiovascular system

Humans are tropical animals and adjusting to increased temperatures is not a problem as long as they can produce enough sweat and the environment permits evaporation of that sweat (Kenney et al. 2014). Still, the thermoregulatory homeostasis at extreme temperatures is only sustainable during short periods of time.

A healthy human body attempts to maintain a core temperature at near-constant level (about 37°C), irrespectively of environmental temperature (Kenny et al. 2010). Cutaneous vasodilation, which increases the skin blood flow in a warm environment, is an adaptive response that brings the metabolic heat to the body surface and in this way facilitates the transfer of heat to the surrounding environment (Morrison et al. 2011). In addition, evaporation of sweat from skin surface is important for heat loss. The sweat response, is however dependent on the cutaneous vasodilation, as it provides blood plasma as the necessary precursor fluid for sweat production (Smith and Johnson 2016). In humans, increased blood flow in the skin is accompanied by a vasoconstriction (decreased blood flow) in visceral organs (Morrison et al. 2011). To compensate for the decreased blood flow in visceral areas an increase in cardiac output (allowing sufficient delivery of oxygen to inner organs) is necessary (Kenny et al. 2010). As the production of sweat requires water, adaptive thermoregulation is also dependent on adequate hydration. Thirst is the body's defense mechanism in response to central perception of a deficit of body fluids. Key physiological signals for thirst are increased plasma osmolality and hypovolemia (decrease in volume of blood plasma) (Koch and Fulop 2017; Meillard-Stafford et al. 2012).

When the human thermoregulatory mechanisms are overwhelmed, exposure to environmental heat stress can give rise to various heat illnesses. Heat illness may be caused by a combination of increased core temperature, dehydration and salt depletion and range from minor heat syncope to severe heat strokes (Fink et al. 2015). Heat syncope/heat fainting entails a short period of unconsciousness due to a sudden drop in blood pressure. Heatstroke is an acute condition occurring when body temperature rises above 40°C. However, mortalities and hospitalisation due to direct heat-related illnesses, such as heat exhaustion and heat stroke, are rare and much less common than hospitalisation and mortality for heat-induced exacerbation of underlying medical conditions (Schmeltz et al. 2016).

Heat is hard on the circulatory system. As mentioned above, heat-related thermoregulatory vasodilation is accompanied by increased heart rate and decreased blood pressure (Fink et al. 2015). Several studies have reported that increased heart rate by itself is associated with increased risk for cardiovascular events (Boersma et al. 2000; Granger et al. 2003; Fox et al. 2008; Palatini and Julius 2004). In hot environments, thus, increased cardiac output and increased skin blood flow significantly rise the cardiovascular demands (Kenney et al. 2014). In addition, prolonged sweating leads to changes in blood properties, in form of reduced plasma volume, increased counts of red blood cells, neutrophils and platelets in circulation, and increased plasma viscosity – all of which contribute to increased susceptibility to cardio- and cerebrovascular death and acute coronary events (Keatinge et al. 1986; McArthur et al. 2010). The physiological strain of heat becomes particularly high when the hot weather lasts for several consecutive days (Rocklöv et al. 2010), especially in cases, when the night temperatures are too high to allow recovery from heat stress (Lubczyńska et al. 2015).

## Heat, heart and the elderly

Old age is a well-known health risk factor during heat waves. During the 2003 heatwave in Italy, for example, 92 % of excess deaths were observed among persons older than 74 years of age (Conti et al. 2005 and 2007). Numerous other epidemiological studies, from all over the world, have confirmed that the risk of heat-related mortality significantly increases with age (Kovats and Hajat 2008; Kenney et al. 2014; Åström et al. 2011). This vulnerability of the elderly has several reasons. Firstly, the likelihood for suffering from and being medicated for various chronic diseases increases with age. Decreased capacity to adaptive thermoregulatory processes, such as increasing the skin blood flow, producing enough sweat and sensing/signalling dehydration is associated with several types of chronic pathologies such as hypercholesterolemia, diabetes and hypertension, as well as with use of many common medications (Kenny et al. 2010; Fink et al. 2015). Accordingly, Fink et al. (2015) reported that in individuals older than 65 years that are diagnosed with a pre-existing illness, the physiological response to heat is more intense (entailing greater changes in both heart rate and mean arterial pressure) and occur at lower temperatures than in the elderly without pre-existing illness. Secondly, studies show that even healthy older adults have an altered cardiovascular response to heat, and thus impaired thermoregulatory capacity, compared to the younger individuals (Kenney et al. 2014; Minson et al. 1998).

To aid thermoregulation, during heat stress the blood volume is redistributed from central to peripheral circulation entailing increased ventricular work to pump blood at profoundly reduced filling pressure (Kenny et al. 2010). Minson et al. (1998) observed that while, during passive heating, the subcutaneous blood flow in young men increased on average about 5.8 l/min, in older men this increase was only about 2.7 l/min. In young men, both the increased cardiac output (4.8 l/min) and the redistribution of blood from the splanchnic and renal circulation (1 l/min) contributed to the increase in subcutaneous blood flow. In the older individuals, however, an attenuated increase in cardiac output (2 l/m) in combination with a reduced capacity to redistribute splanchnic and renal blood flow (0.7 l/m) was observed (Minson et al. 1998).

Reduced ability to maintain stroke volume is one of the main reasons behind the attenuated increase in cardiac output during passive heating in older individuals. At prolonged heat exposure, central venous pressure (CVP) falls in both old and young subjects, according to results of a study of 12 healthy men of varying age (Minson et al. 1998). However, while the younger men were able to maintain stroke volume by increasing contractility, the stroke volume declined progressively in the older individuals (Minson et al. 1998). As the heart rate as a percentage of maximum was higher in older individuals, at any given CVP, the older subjects relied more on their ability to increase heart rate than the younger ones did. Thus, exposure to heat in the elderly entails both excess central cardiovascular strain and an attenuated increase in thermoregulatory skin blood flow. In addition, aging is associated with decreased sweat rate and decreased sweat output per gland (Minson et al. 1998; Anderson and Kenney 1987; Inoue 1996; Smith et al. 2013) leading to diminished evaporative heat loss, which may exacerbate the cardiovascular strain even more (Kenney et al. 2014).



## Evidence for heat effects on cardiovascular health in epidemiological studies

During the last 25 years, health effects of severe heat waves have received considerable attention, due to the large numbers of excess cases of death. For example, the number of deaths during the 1995 Chicago heatwave showed an increase by more than 700 excess cases, compared to the same period in the previous year (Whitman et al. 1997). The 2003 European heat wave may have caused as many as 70,000 excess deaths across European continent (Robine et al. 2008), while the 2010 Moscow heat wave is thought to have increased the mortality by more than 11,000 cases (Shaposhnikov et al. 2014). Thus, it is not surprising that the majority of heat wave studies have concentrated on impacts on mortality, while different morbidity outcomes are less common (Li et al. 2015). However, the data available today generally suggest that increase in morbidity, measured for example as hospital admissions during heatwaves, is not as severe as the effect on mortality. One explanation to this is that people who die during heatwaves, die rather suddenly, and therefore do not reach the attention of the medical services (Kovats and Hajat 2008; Mastrangelo et al. 2007).

### Epidemiological assessment of health effects related to high temperatures

Several different approaches are used in the epidemiological research to study health effects related to high temperatures. One of the most common ones is assessment of health outcomes related to a specific time period defined as the heatwave. The definition of a “heatwave” is, however, rather vague and different criteria may be used in different studies. Generally, it refers to a period of unusually hot weather (e.g.  $\geq 2$  days with temperature  $\geq 95^{\text{th}}$  or  $98^{\text{th}}$  percentile) for a specific region (Xu et al. 2016). The health impacts of heatwaves are traditionally investigated by comparing the number of cases occurring during a heatwave with a baseline value from, for example, the same time period in previous years (e.g. Kovats and Hajat 2008; Whitman et al. 1997; Anderson and Bell 2011; Vandentorren et al. 2004; MacFarlane and Waller 1976).

Another approach is assessing the associations between health effects and changes in temperature over time (e.g. associations between daily death counts and the daily average temperatures over a number of years). Time-series regression models are often used to quantify the temperature-health outcome relationships (e.g. Wu et al. 2013; Hajat et al. 2002; Armstrong et al. 2009; Braga et al. 2002; Keatinge et al. 2000). In cases when person-level data are available, case-crossover design (in which the date of health incident is considered a case, and proximate days are used as controls) may be used (e.g. Stafoggia et al. 2008; Lubczyńska et al. 2015; Stafoggia et al. 2006). Some health effects of high temperatures may, however, have a “lag time”, i.e. be delayed by up to a few days. These lag patterns are known to vary across regions and diseases; and thus, multiple lag definitions may be inserted into statistical models (Li et al. 2015).

Several groups of cause-specific mortalities/morbidities may be assessed in temperature effect studies. Cardiovascular causes are among the most frequently investigated ones on the topic. The definition of ‘cardiovascular’ health outcomes may, however, vary between epidemiological investigations. Most often ‘cardiovascular’ mortality/morbidity includes all circulatory system diseases (i.e. ICD-10, I00–I99) ranging from ‘hypertensive diseases’ to ‘cerebrovascular’ health outcomes (e.g. Schmeltz et al. 2015; Lubczyńska et al. 2015; Sherbakov et al. 2018; Yang et al. 2015). Occasionally, however, cardiac and cerebrovascular

illnesses are reported separately (e.g. Stafoggia et al. 2006; Nitschke et al. 2007; Wang et al. 2012). More seldom, cardiac and respiratory outcomes are pooled as ‘cardiorespiratory’ illnesses (Xu et al. 2016).

### Cardiovascular mortality

Epidemiological studies have provided plentiful evidence for that various cardiovascular conditions are among the prominent underlying causes of mortality during heatwaves worldwide (e.g. Lubczyńska et al. 2015; Åström et al. 2011; Stafoggia et al. 2006; Yang et al. 2015; Wang et al. 2012; Turner et al. 2013; Huyen et al. 2001; Sheridan and Lin 2014; Huang et al. 2012; Baccini et al. 2008; Basu 2009; McMichael et al. 2008; Guo et al. 2014). An increased risk of dying on hot days has, for example, been reported in individuals with ischaemic heart disease, as well as for other cardiovascular conditions such as congestive heart failure, conduction disorders, and cerebrovascular diseases (Åström et al. 2015). High temperature has also been shown to increase the risk for an acute MI (Madrigano et al. 2013). During the Paris 2003 heatwave, the number of out of hospital cardiac arrests was reported to increase 2.5 fold compared to the reference periods (Empana et al. 2009).

Lubczyńska et al. (2015) assessed the relationship between cardiovascular mortality risk and air temperature in Cyprus and found a significant association with heat for both cerebrovascular diseases, and ischaemic and other heart diseases. The authors observed that while the RR for dying from cardiovascular ill health was highest on the day of the heat event, it remained significantly elevated for another day. The associations between high temperatures and mortality were consistent regardless whether the authors used minimum, maximum, or mean temperatures, although the effect was more pronounced for the mean temperatures, which supports the suggestion that consecutive high day- and night-time temperatures are the most hazardous for cardiovascular mortality (Lubczyńska et al. 2015).

Baccini et al. (2008) investigated the effect of temperature on daily mortality in 15 European cities and found a typical V-shaped temperature-response relationship, with a change-point (the shift from “cold”-related effects to “heat”-related effects) that varied among cities. From meta-analyses, the authors estimated that the threshold (daily maximum) temperature for heat-related mortality was on average 29°C for Mediterranean cities and about 23°C for North-Continental cities. Further, they estimated that the overall change in all natural mortality associated with a 1°C increase in maximum apparent temperature above the city-specific threshold was on average 3.12 % in the Mediterranean region and 1.84 % in the North-Continental region. Cardiovascular mortality increased with 4.7 % (per 1°C increase in maximum apparent temperature) in Mediterranean cities whereas in North-Continental cities no significant increase in cardiovascular mortality was detected. In general, Baccini et al. observed stronger associations between heat and mortality from respiratory diseases than from cardiovascular ones (Baccini et al. 2008). In a later study, Rocklöv et al. (2010) found that the cardiovascular mortality in a Nordic population (Stockholm County, Sweden), was mainly associated with an extreme exposure to heat (apparent maximum temperature >98<sup>th</sup> percentile, or 27.6°C).

Another multi-country study by McMichael et al. (2008) described heat and cold-related mortality in 12 low- and middle-income countries and found that most cities showed a U-shaped temperature mortality relationship. Threshold temperatures for heat-related cardiorespiratory mortality in this study ranged from 15–30°C and were higher in cities with

warmer climates. The percentage increase in cardiorespiratory mortality for each degree above the “heat threshold” varied from about 1 % in Mexico City to 17.6 % in Monterrey. The authors could not explain these differences between cities by any demographic or economic factors, although, the low number of the cities included limited the statistical power. Yang et al. (2015) compared the effect of temperature on cardiovascular mortality in 26 Chinese regions and identified three factors, which directly affected the exposure-outcome relationship. These factors included the number of available hospital beds, the percentage of population engaged in industrial occupations, and the percentage of women in the region.

Åström et al. (2015) used data from Rome, Italy, and Stockholm, Sweden, to evaluate the effect of heat waves on mortality in five subgroups of chronically ill individuals, diagnosed with either congestive heart failure, chronic obstructive pulmonary disease (COPD), diabetes, or psychiatric disorders, as well as survivors of MI. In both cities, mortality in all investigated subgroups was significantly increased during heatwave days compared to non-heatwave days. In Rome, this increase ranged from 7 % among survivors of MI to 25 % in individuals diagnosed with COPD and diabetes. In Stockholm, the range of increased mortality was from 10 % for congestive heart failure to 33 % for the psychiatric subgroup.

### Morbidity

While the evidence for associations between high temperatures and increased cardiovascular mortality is rather strong, for cardiovascular morbidity the results remain inconsistent (Li et al. 2015). Some investigations do report that high temperatures affect cardiovascular morbidity. For example, in Ho Chi Minh City, Vietnam, the overall risk of cardiovascular hospital admissions increased with about 13 % during heatwave events (defined as temperature  $\geq$  the 99<sup>th</sup> percentile for  $\geq 2$  consecutive days) year 2004–2013 (Phung et al. 2016). The exposure-response curve in this study was J-shaped with a threshold temperature of about 30°C. In Adelaide, Australia, the hospital admission of ischaemic heart disease increased by 8 % among people aged 65–74 years during heatwaves that took place between 1993 and 2006 (Nitschke et al. 2007), and showed a marked increase during the 2009 heatwave in the 15–64-year age group (Nitschke et al. 2011). In certain regions of California, USA, an increase in emergency room visits due to cardiovascular causes was observed during the 2006 heatwave (about 5 % in the Central Coast region) (Knowlton et al. 2009).

Most European studies, on the other hand, have not been able to show any such relationship between heat and cardiovascular illness. For example, a report assessing the effects of both cold and warm spells on cardiovascular emergency hospitalization in Mediterranean region, only found increased incidence rate ratios during cold spells and not during heatwaves (Ponjoan et al. 2017). Michelozzi et al. who investigated the heat effects on the number of hospital admissions in 12 European cities within the period 1990 to 2001, detected a heat-related increase in respiratory admissions in both Mediterranean and North-Continental cities, while the number of cardiovascular and cerebrovascular admissions tended to be negatively related to heat or not related at all (Michelozzi et al. 2009). Similarly, both an Italian (Mastrangelo et al. 2007) and a Dutch (van Loenhout et al. 2016) study observed an increase in respiratory hospital admissions during periods with high temperatures, but did not detect any noticeable effect on circulatory diseases. Studies from Sweden have also confirmed the stronger

relationship between respiratory admissions and high temperatures than between cardiovascular illness and heat (Rocklöv and Forsberg 2009).

The excess of circulatory disease reported by mortality studies, but not by morbidity studies, may support the hypothesis that deaths from circulatory disease occur rapidly before people reach a hospital (Mastrangelo et al. 2006). It is possible, that a very rapid development of disease states combined with fatigue and disorientation make people less likely to seek help and therefore die at home.

### Incidence of stroke

A small number of studies have reported an increase in stroke incidence at higher ambient temperatures (McArthur et al. 2010). Berginer et al. (1989) reported that the average daily incidence of stroke was about twice as great on relatively warm days as on relatively cold ones in Beer-Sheva, Israel. In western Scotland, every 1°C increase in mean temperature during the preceding 24h was shown to be associated with a 2.1 % increase in ischemic stroke admissions. In Brisbane, Australia the average daily primary intracerebral haemorrhage emergency admissions increased by 15 % for a 1°C increase in daily maximum temperature for the group aged 65 years or more, while the temperature effect on ischemic stroke was negative (Wang et al. 2009). Ha et al. (2014) found that increased risk for stroke hospitalisation (especially for ischemic stroke hospitalisation) in Pennsylvania, USA, was significantly associated with both heat day (any day with a mean temperature exceeding the 95<sup>th</sup> percentile) and heatwave (any period with at least two consecutive heat days) at a 2-day lag. Other studies associating heat with stroke, have, however, shown conflicting results by finding either negative/mixed associations (Wang et al. 2009; Chang et al. 2004; Goggins et al. 2012; Hong et al. 2003; Liu et al. 2004; Mostofsky et al. 2014; Çevik et al. 2015) or no associations at all (Field and Hill 2002; Kyobutungi et al. 2005). A systematic review from 2016 (Wang et al. 2016) found some evidence for that lower mean temperatures are associated with increased risk for intracerebral haemorrhage (but not for ischemic stroke nor subarachnoid haemorrhage), but did not report any evidence to support increased risk for occurrence of stroke during periods of hot weather.

### Conclusions and research needs

Biologically plausible associations exist between high temperatures and risks for cardiovascular illness and death. In the elderly especially, the increased cardiovascular demand during periods of hot weather may severely increase the risk of mortality. However, while the evidence for associations between high temperatures and increased cardiovascular mortality is rather strong, for cardiovascular morbidity the results remain inconsistent. More studies are needed to establish whether high temperatures increase risk of cardiac and cerebrovascular illnesses.

In the developed world, the average life span is increasing, and consequently, issues associated with old age are becoming a major challenge in modern societies (Social Development 2002). With the rapidly growing numbers of elderly worldwide, the number of people at risk of illness and death during a heatwave, and thus the number of potential causalities, also increases.

It is also important to stress that, even when the relationship between high temperatures and human cardiovascular mortality has been established as a global phenomenon, epidemiological investigations indicate that there are rather region-specific variations in heat sensitivity, coping capacity, and adaptation measures in different populations. Consequently, extrapolating the relationships between temperature and health outcomes, reported for one region, directly to other regions is likely to introduce substantial errors (Lubczyńska et al. 2015). Thus, when estimating the temperature-related health risks, the calculations should be as location-specific as possible.

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## 8. Common occupational chemical exposures

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In 2017, the SBU reviewed the epidemiological literature on chemical occupational exposure and heart disease (SBU 2017). The review found evidence that several occupational exposures were associated with an increased risk of heart disease, among them three very wide-spread workplaces exposures: silica dust, engine exhaust and welding fumes. The Agency does not consider clinical and experimental studies in their evaluation. This chapter is focused on these three common occupational exposures, in order to further evaluate evidence for causality, discuss mechanisms and evaluate dose-response, considering evidence both from epidemiological and experimental studies.

The chapter is divided into three sections: I) Crystalline silica, II) Diesel motor exhaust, and III) Welding fumes.

### Section I: Crystalline silica

Exposure to respirable crystalline silica (RCS) is one of the most common hazardous air pollutants in the occupational environment. In the EU 5.5 million workers are regularly exposed to RCS. In Sweden, around 90,000 to 150,000 workers are exposed, most of them in the construction sector.

Inhalation of RCS induces a chronic inflammation in the lung and may cause COPD and lung fibrosis (silicosis). The chronic inflammation is partly believed to be caused by the reactive surface of the particles, and the effect is more pronounced when the surface is fresh. The particles have a long retention in the lung and continue to induce an active response also after external exposure has ceased. RCS also modifies immune response, down-regulating cell-mediated immunity (increasing the risk for tuberculosis), and increasing the risk for autoimmune disease (Swedish Criteria Group for Occupational Standards 2014). Several studies have also indicated an increased risk for renal disease (OSHA 2016; Swedish Criteria Group for Occupational Standards 2014). Exposure to RCS is classified as a human carcinogen based on an increased risk for lung cancer (IARC 1997).

It is well established that cohorts of workers exposed to RCS have an increased risk of cor pulmonale (heart disease secondary to pulmonary disease). Recently, the possibility of an increased risk for primary CVD (IHD and stroke) has received more attention, partly due to increasing evidence for causal associations with agents causing chronic inflammation.

Based on a systematic review of epidemiological studies of workplace exposure to RCS, the SBU (2017) concluded that there is limited evidence for an association with IHD (8 included studies: Ahlman et al. 1991; Björ et al. 2010; Graham et al. 2004; Koskela et al. 2005; Kreuzer et al. 2015; Liu et al. 2014; Murray et al. 1993; Reid and Sluis-Cremer 1996), moderate evidence for associations with pulmonary heart disease (4 studies: Liu 2014; Murray 1993; Reid and Sluis-Cremer 1996; Vermeulen et al. 1978), and insufficient evidence for an

association with stroke (3 studies: Kreuzer et al. 2015; Reid and Sluis-Cremer 1996; Peters et al. 2013).

This review will focus on the studies of primary CVD reporting data which can be used to evaluate dose-response associations. Three (Björ et al. 2010; Kreuzer et al. 2015; Liu et al. 2014) of the nine studies reviewed below, and listed in Table 3, were included in the SBU evaluation and five (Fan et al. 2018; Gellisen et al. 2018; Lai et al. 2018; Liu et al. 2017; Wiebert et al. 2017<sup>1</sup>) have been published afterwards. Chen et al. (2012) was not included in the SBU (2017) review.

### Dose-response associations in epidemiological studies

Björ et al. (2010) studied 13,621 male Swedish miners and the association between cumulative exposure to respirable dust (on average 2.5 % silica, range 2.0 %–3.0 %<sup>2</sup>), as estimated from a job-exposure matrix (JEM) based on occupation, and mortality from MI. A significantly increased risk was observed for 35–100 mg respirable dust/m<sup>3</sup>-years (ys) (Table 3), and further increased for exposure to  $\geq 100$  mg/m<sup>3</sup>-ys. This would correspond to approximate cumulative crystalline silica exposures of  $>0.9$ –2.5 mg/m<sup>3</sup>-ys and  $\geq 2.5$  mg/m<sup>3</sup>-ys, respectively.

Kreuzer et al. (2015) investigated cause-specific mortality in German uranium millers (n=4,054), employed for at least 6 months 1946–1990. Exposure assessment for RCS was based on measurements performed from 1960 and on, and a JEM was constructed based on extensive earlier measurements (n=93,000) converted to respirable dust and RCS concentrations after extensive parallel sampling and reconstruction of historical work situations and ventilation. Median RCS exposure was 2.5 mg/m<sup>3</sup>-ys and maximum exposure 37 mg/m<sup>3</sup>-ys. Comparison with the general population showed an overall decrease in both total mortality and mortality from IHD, while deaths from stroke did not differ from the expected. Internal dose-response analyses (cumulative RCS exposure lagged 5 years) showed no association with IHD or stroke.

In a case-control study of RCS exposure and MI, nested within the cohort of German uranium millers, Gellissen et al. (2019) included 292 cases of first MI occurring while still employed and <65 years of age, and individually matched (date of birth, period of hire, 3:1) controls. Cumulative RCS exposure was lagged five years as in Kreuzer et al. (2015). Subjects were subdivided by likelihood of significant exposure misclassification from pre-hire to RCS during e.g. coal mining, military service or internment as prisoner of war, where those born 1929 or later and hired 1946–1954 were considered to have the least misclassification from such exposure, the largest exposure at young age, and longest follow-up. Using the lowest tertile of exposure (up to 5.74 mg/m<sup>3</sup>-ys) as the reference, no overall increase in risk for MI was found in the highest tertile or in linear analyses, but an increase was observed in the intermediate tertile (5.74–14.62 mg/m<sup>3</sup>-ys). However, when the analysis was restricted to the sub-cohort considered to have least misclassification from pre-hire exposure, elevated ORs were observed in both the intermediate and highest tertiles.

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<sup>1</sup> Conference abstract

<sup>2</sup> Based on 3,122 measurements (Hedlund et al. 2008)

A series of studies of metal mine and pottery factory workers in China explored associations between cumulative exposure to RCS and CVD. Based on total dust measurements, historical bulk samples, and parallel sampling of RCS, facility-, job- and calendar-year-specific RCS concentrations were used to create a JEM. The complete work history from employee rosters was used to calculate the cumulative exposure and maximum annual mean exposure for each worker. The experience of the full cohort of 74,040 workers was reported by Chen et al. (2012), who found an increasing risk for pulmonary heart disease with increasing exposure to RCS, but inverse trends for hypertensive heart disease and IHD. However, in subanalyses restricted to workers who never had been exposed  $>0.1 \text{ mg/m}^3$ , and adjusted for smoking, they still observed significant dose-response associations for pulmonary heart disease. In this subgroup such associations were also observed for IHD.

These findings were further explored by Liu et al. (2014 and 2017). Liu et al. (2014) restricted the cohort to workers with full work histories and/or information on smoking habits, and found a linear dose-response association between cumulative RCS exposure and IHD among workers exposed to  $\leq 0.1 \text{ mg/m}^3$ .

The effect on cardiovascular and cerebrovascular disease from low-dose exposure to RCS was further targeted in Liu et al. (2017). Within the cohort of Chinese metal mine and pottery factory workers, they selected workers who had never had an annual mean exposure to RCS exceeding  $0.35 \text{ mg/m}^3$ ,  $0.1 \text{ mg/m}^3$ , and  $0.05 \text{ mg/m}^3$ , respectively. Dose-response associations with cumulative dose were explored within each of the three strata. The analyses were adjusted for smoking habits (available for 67 % of the cohort). Significant dose-response associations were found between cumulative dose and IHD for all three strata of lifetime highest mean annual exposure level, with increased risks in the highest quartiles (above around  $0.7\text{--}0.9 \text{ mg/m}^3\text{-ys}$ ). The association was somewhat steeper for the lower life-time mean annual exposure category. Conversely, dose-response associations with pulmonary heart disease were evident only for the two highest categories of annual lifetime exposure. No overall increase or dose-response associations were discerned for cerebrovascular disease.

Lai et al. (2018) focused on workers ( $n=7,665$ ) from one of the mines within the cohort of Chinese metal mine and pottery factory workers. Job histories were available from company records and job title was linked to a job and calendar-year specific JEM for RCS exposure. In all, 47.7 % of the cohort was exposed to RCS during their working period and was further divided into tertiles based on cumulative exposure to RCS. Internal analysis showed an increased risk for IHD mortality in the medium ( $0.49\text{--}0.84 \text{ mg/m}^3\text{-ys}$ ; HR 1.54, 95 % CI 1.06–2.23) and highest ( $0.84 \text{ mg/m}^3\text{-ys}$  or higher; HR 1.78, 95 % CI 1.28–2.48) tertiles, with a significant trend across categories ( $p<0.001$ ) but a borderline finding for the continuous analysis (HR per  $1 \text{ mg/m}^3\text{-ys}$  increase in cumulative exposure: 1.13, 95 % CI 0.99–1.30). The risk for pulmonary heart disease was significantly increased in the highest tertile. No increase in risk was observed for cerebrovascular disease. The results were unchanged in a sensitivity analysis excluding workers who started work before the start of dust monitoring in 1950. After adjustment for potential confounders and smoking RCS exposure was estimated to account for 17.5% of the mortality from CVD in the cohort. It is noteworthy the exposure intensities to RCS were moderate in this cohort, on average  $0.02 (\pm 0.002) \text{ mg/m}^3$  in the low tertile,  $0.03 (\pm 0.01) \text{ mg/m}^3$  in the medium, and  $0.06 (\pm 0.06) \text{ mg/m}^3$  in the high tertile.

Wiebert et al. (2017) reported preliminary data (conference abstract) on the incidence of MI (hospital admissions and deaths) in the total Swedish population of manual workers in 1980 in relation to cumulative exposure to RCS. Occupational title 1960 to 1990 was linked to a JEM to assess lifetime exposure to RCS. No smoking information was available. Ever exposure to RCS was associated with a significantly increased risk for MI, more so among women than among men. An increasing risk for each quartile of exposure was observed in both genders. In the highest quartile of cumulative exposure ( $\geq 1.54$  mg/m<sup>3</sup>-ys; Wiebert P personal communication) the HR (adjusted for age, socioeconomic index and urbanity) was 1.66 (95 % CI 1.27–2.18) for women, and 1.06 (95 % CI 1.03–1.10) for men, respectively.

Fan et al. (2018) studied CVD morbidity and mortality in 2,551 male foundry workers in Sweden who had been employed for at least one year 1913–2005. Cumulative exposure to RCS was estimated from 1,667 measurements performed 1968 and on for each job category based on mixed models, and linked to company personnel records. The cohort was followed from 1987 to 2012, and the mortality/morbidity was compared to that of the total Swedish population. (Of the originally retrieved cohort of 4,603 workers, 477 workers were excluded due to incomplete personnel records and 497 died or emigrated before 1987). Morbidity data were used for stratification by quartiles of cumulative exposure and duration of employment. An overall increase in cardiovascular mortality was observed, with an increase in deaths due to stroke. Morbidity in stroke was overall higher than expected but showed no exposure-effect association with increasing quartiles of cumulative dose, nor with duration of employment. The mortality from acute MI was lower than expected, but the incidence of MI was not significantly different from the general population and dose-response associations with cumulative exposure or duration of employment was not displayed. No adjustment was possible for other exposures at the foundries. Information on smoking habits was not available. Although the exposure assessment for RCS is strong, the study is considered inconclusive due to a long gap from entry into exposure until start of follow-up (close to 500 excluded deaths out of a total of 1,200) potentially introducing a substantial survivor effect, and the lack of a sensitivity analysis for excluded workers with incomplete work histories.

## Discussion and conclusion

The largest fully published study so far which provides dose-response data is Björ et al. (2010), who found a statistically significant increased mortality from MI for cumulative RCS doses of 0.9–2.5 mg/m<sup>3</sup>-ys. Annual mean exposure levels were 0.1–0.4 mg/m<sup>3</sup> in 1968–1973, but dropped to <0.05 mg/m<sup>3</sup> after 1975 due to precautionary measures (Hedlund et al. 2007). Another Swedish study of the full manual worker population in Sweden in 1980 supports this conclusion, with dose-response findings and significantly increased MI mortality for cumulative RCS doses of 1.54 mg/m<sup>3</sup>-ys and up in both genders. The Chinese studies have systematically explored the hypothesis that MI is associated with cumulative exposure to RCS at low air concentrations, but is superseded by competing risks at higher air levels. The study by Liu et al. (2017) supports such associations up to annual mean concentrations of 0.1 mg/m<sup>3</sup>, but with somewhat steeper associations for the lowest air concentrations (0.1 mg/m<sup>3</sup> and 0.05 mg/m<sup>3</sup>, respectively, as highest lifetime annual means). A recent study of a subgroup of Chinese miners with overall moderate exposure intensities to RCS seems to fit in with this pattern suggesting an increased risk by cumulative exposure already from the interval 0.49–

0.84 mg/m<sup>3</sup>-ys (Lai et al. 2018). A small case-control study observed an increased risk for MI in a subgroup with high exposure and long follow-up (Gellisen et al. 2019), but these results should be interpreted with care.

Two smaller studies (Fan et al. 2018; Kreuzer et al. 2015) did not find support for an increased risk for IHD associated with exposure to RCS, but it can be questioned if the study by Fan et al. (2018) is conclusive for reasons stated above.

The studies have generally had limited possibilities to adjust for individual risk factors for CVD, although several could adjust for smoking. However, all studies except Fan et al. (2018) were based on internal analyses. The Chinese studies included subanalyses restricted to subjects with information on individual smoking habits with little indication of confounding.

In general, much effort has been put into reconstructing the full work histories. However, historical measurements of RCS were often not available and thus RCS exposure was reconstructed (often using parallel sampling) from e.g. measurements of respirable dust, or short-term measurements.

Possible gender differences have not been systematically explored. It is noteworthy that Wiebert et al. (2017) observed a steeper dose-response association between RCS and risk for MI among women than among men.

RCS exposure generally occurs as a component of other dust, e.g. in mining as a component of dust from the rock, in pottery as a component of the clay, and in construction as part of concrete dust. These components have generally not been separated. Here, evidence from experimental data (below) is important for the interpretation.

None of the included studies supported dose-response associations between exposure to RCS and stroke, although an overall increase in morbidity was observed by Fan et al. (2018).

In conclusion, data from four large cohorts, reflecting different exposure circumstances, suggest that exposure to RCS increases the risk for MI even following quite low exposure intensities (<0.05 mg/m<sup>3</sup>, Liu et al. 2017) corresponding to half the current Swedish (and EU) occupational exposure limit. Furthermore, excess risk was observed at cumulative doses of only 0.5–2.5 mg/m<sup>3</sup>-ys (0.49–0.84 mg/m<sup>3</sup>-ys, Lai et al. 2018; >0.7 mg/m<sup>3</sup>-ys, Liu et al. 2017; 0.9–2.5 mg/m<sup>3</sup>-ys, Björ et al. 2010; ≥1.54 mg/m<sup>3</sup>-ys, Wiebert et al. 2017). Assuming that a full working life may be 45–50 years, the average intensity of exposure would need to be kept below 0.025 mg/m<sup>3</sup> in order not to reach these cumulative doses.

### Implications for practice

Exposure to RCS is associated with an increased risk for MI at low exposure intensities and low cumulative doses implicating a need for workplace measures to reduce exposure as much as possible as well as a revision of the standard for occupational exposure to 0.025 mg/m<sup>3</sup>. This is in accordance with recommendations by the Scientific Committee on Occupational Exposure Limits (SCOEL) and the American Conference of Governmental Industrial Hygienists (ACGIH) based on other end-points (malignant and non-malignant respiratory disease).

Table 3. Dose-response associations between exposure to respirable crystalline silica (RCS) and cardiovascular disease.

Author	Outcome	Exposure	Result	Comment
Björ et al. 2010	MI mortality 14,77 cases (1,166 exposed) among 13,621 men followed 1952–2001.	Iron-ore mining. Respirable dust measured 1968– 1995 (1,981 samples). Mean RCS content 2.5 % (range 2.0–3.0 %). Geometric mean respirable dust (range) for all work categories: 1968– 1973: 3.0 mg/m <sup>3</sup> (0.1–25 mg/m <sup>3</sup> ), 1974–1995: 0.5 mg/m <sup>3</sup> (0.3–3.0 mg/m <sup>3</sup> ). Cumulative exposure assessed (JEM) from the 1920- ies.	<i>All:</i> Not exposed: RR 1 (reference), >0–35 mg <sup>3</sup> -ys: RR=0.98 (0.85–1.15), >35–100 mg <sup>3</sup> -ys: RR 1.21 (1.03– 1.40), >100 mg <sup>3</sup> -ys: RR 1.31 (1.13– 1.52)  <i>Attained age ≤60:</i> Not exposed: RR 1 (reference), >0–35 mg <sup>3</sup> -ys: RR 0.93 (0.71–1.23), >35–100 mg <sup>3</sup> -ys: RR 1.36 (1.01–1.84), >100 mg <sup>3</sup> -ys: RR 1.82 (1.33–2.49)  <i>Attained age &gt;60:</i> Not exposed: RR 1 (reference), >0–35 mg <sup>3</sup> -ys: RR 1.04 (0.87–1.25), >35–100 mg <sup>3</sup> -ys: RR 1.12 (0.94–1.34), >100 mg <sup>3</sup> -ys: RR 1.16 (0.98–1.37)	Internal comparison. Poisson regression. Exposure to diesel engine exhaust. No individual smoking data.
Chen et al. 2012	IHD mortality (ICD10: I20– I25; n=624), pulmonary heart diseases (I26–I27; n=2,729), and hyper- tensive heart disease (I11, n=391). A cohort of mainly male workers (n=74,040) followed 1960–1993 (median follow-up 33 ys).	Workers from 20 metal mines and 9 pottery factories in China, employed for at least 1 year 1960– 1974, JEM based on 4,200,000 environmental samples 1950–2003 (see also below Liu et al. 2017). 67 % of the workers were exposed to RCS, mean RCS exposure among the exposed was 0.2 mg/m <sup>3</sup> , 22 % of the exposed workers had pneumoconiosis.	Total cohort (HR increase per 1 mg/m <sup>3</sup> -ys of cumulative exposure to RCS): Pulmonary heart disease 1.05 (1.04–1.06); Hypertensive heart disease: 0.98 (0.96–1.00); IHD: 0.97 (0.95–0.99)  Workers with lifetime exposure to RCS <0.1 mg/m <sup>3</sup> (increase in death rate per 1 mg/m <sup>3</sup> -ys of cumulative exposure to RCS): Pulmonary heart disease 6 % (no CI given), IHD: 4 % (no CI given). The analyses were adjusted for smoking.	Internal Cox regression analyses adjusted for age and year at hire, and facility. Subanalyses were adjusted for smoking.
Liu et al. 2014	IHD mortality (ICD10: I20– I25; n=496), pulmonary	Population as above, but restricted to those with detailed data on yearly work history and/or	In the total cohort, mortality rates from pulmonary heart disease increased monotonically with cumulative exposure. In contrast, IHD increased initially, but then	Internal analyses. Cox regression. Penalized spline models were



	heart diseases (I26–I27; n=1,528), and hypertensive heart disease (I11, n=322). A cohort of mainly male workers (n=74,040) followed 1960–1993 (median follow-up 33 ys).	smoking (n=42,572). Mean duration of follow-up 34.6 ys, cumulative exposure to RCS mean 3.7 mg/m <sup>3</sup> -ys, 14 % of the workers had silicosis.	decreased in the highest quartile. Stratification by lifetime highest exposure to RCS showed a negative trend with each quartile of cumulative RCS in the >0.1 mg/m <sup>3</sup> stratum (HR 1.18, HR 1.05, HR 0.90, HR 0.61, respectively; p (trend)=0.006).  In the ≤0.1mg/m <sup>3</sup> stratum a positive trend with each quartile of exposure was observed (HR 1.04, HR 1.13, HR 1.52, HR 1.60, respectively; p<0.001)  10-year exposure to RCS at 0.1 mg/m <sup>3</sup> was estimated to increase mortality from IHD with 65 %.	used to explore dose-response associations.
Liu et al. 2017	IHD mortality (ICD10: I20–I25; n=384), pulmonary heart disease (I26–I27; n=585), cerebrovascular disease (I60–I69; n=1,522) among 44,807 workers employed ≥1 y 1974–2003, followed through 2003.	Male and female workers in metal mines and pottery factories in China (subcohort of Chen 2012). Cumulative RCS exposure based on individual full work history. Analysis stratified by maximum life-time annual mean RCS level: ≤0.35 mg/m <sup>3</sup> , ≤0.1 mg/m <sup>3</sup> , and ≤0.05 mg/m <sup>3</sup> , respectively.	<i>IHD</i> (by quartile of cumulative RCS dose)  ≤0.05 mg/m <sup>3</sup> maximum annual mean: 0.01–0.26 mg/m <sup>3</sup> -ys: HR 0.81 (0.36–1.85), 0.27–0.47 mg/m <sup>3</sup> -ys: HR 1.15 (0.55–2.41), 0.48–0.67 mg/m <sup>3</sup> -ys: HR 1.61 (0.87–1.61), >0.67 mg/m <sup>3</sup> -ys: HR 1.89 (1.07–3.35)  HR for each 1-ln mg/m <sup>3</sup> increase 1.10 (1.00–1.22)  ≤0.1 mg/m <sup>3</sup> max annual mean: HR for each 1-ln mg/m <sup>3</sup> increase 1.09 (1.02–1.16)  ≤0.35 mg/m <sup>3</sup> max annual mean HR for each 1-ln mg/m <sup>3</sup> increase 1.05 (1.01–1.10)  <i>Cerebrovascular disease</i> : No increase in risk with increasing cumulative exposure in either stratum of maximum mean annual exposure.  <i>Pulmonary heart disease</i> : No dose-response with cumulative exposure for maximum mean annual exposure ≤0.05 mg/m <sup>3</sup> . Significant associations with cumulative dose for both ≤0.1 mg/m <sup>3</sup> and ≤0.35 mg/m <sup>3</sup> as lifetime highest mean annual exposure.	Internal analysis, Cox regression, HR as compared to no exposure. Sensitivity analyses including smoking with similar results for incremental total mortality by cumulative dose. No indication of effect modification by smoking status, gender of type of facility.

Lai et al. 2018	IHD (ICD10: I20–I25) mortality, pulmonary heart disease (I26–I27), and cerebrovascular disease (I60–I69) 1960–2012 among 7,665 (6,542 male) miners (median follow-up 42.5 ys).	Cohort of workers at one iron ore mine (part of larger cohort published by Chen et al. 2012), with cumulative exposure based on job title linked to JEM. 47.7 % of the workers were exposed to RCS (96.2 % male). Tertiles of cumulative exposure among the exposed were: Low ( $\leq 0.49$ mg/m <sup>3</sup> -ys), medium (0.49–0.84 mg/m <sup>3</sup> -ys), high (>0.84 mg/m <sup>3</sup> -ys), with average intensities of 0.02, 0.03, and 0.06 mg/m <sup>3</sup> , respectively.	IHD: Low tertile HR 1.19 (0.74–2.93), medium HR 1.54 (1.06–2.23), high HR 1.78 (1.28–2.48), p for trend <0.001, HR per 1 mg/m <sup>3</sup> -y increase of RCS exposure 1.13 (0.99–1.30).  Pulmonary heart disease: Low tertile HR 0.56 (0.17–1.88), medium HR 1.26 (0.62–2.57), high 2.01 (1.16–3.48); p for trend=0.01, HR per 1 mg/m <sup>3</sup> -y increase of RCS exposure 1.35 (1.20–1.53).  Cerebrovascular disease: Low tertile HR 0.95 (0.67–1.35), medium HR 1.23 (0.95–1.61), high HR 0.95 (0.72–1.23)	Internal comparison with unexposed. Cox regression, adjusted for gender, year at hire, age at hire, and smoking intensity.
Wiebert et al. 2017	Hospital admissions and mortality from MI among all manual workers in the Swedish national census 1980	Life-time cumulative exposure to RCS was estimated from a JEM based on occupational title in censuses 1960–1990	<i>Men</i> : HR ever exposure: 1.02 (1.00–1.04); Highest quartile ( $\geq 1.54$ mg/m <sup>3</sup> -ys): 1.06 (1.03–1.10)  <i>Women</i> : HR ever exposure: 1.29 (1.15–1.46); Highest quartile ( $\geq 1.54$ mg/m <sup>3</sup> -ys): 1.66 (1.27–2.18)  Dose-response for both genders	Internal comparisons, adjusted for age, socioeconomic status and urbanity. No smoking data.
Fan et al. 2018	Mortality/morbidity 1987–2012 in MI (ICD10: I21–I22; n=100/311) and stroke (I61, I63, I64; n=47/327) in 2,551 male Swedish foundry workers entering employment in 1913–2005	Cumulative exposure to RCS was estimated from 1,667 measurements performed 1968 and on for each job category based on mixed models	MI (morbidity; SIR) by quartile of cumulative dose (mg/m <sup>3</sup> -ys): <0.11: 1.0 (0.7–1.4); 0.11–0.25: 1.3 (1.0–1.6); 0.25–0.65: 0.8 (0.7–1.1); >0.65: 1.0 (0.8–1.2)  Stroke (morbidity; SIR) by quartile of cumulative dose (mg/m <sup>3</sup> -ys): <0.11: 1.4 (1.0–2.0); 0.11–0.25: 1.5 (1.1–1.9); 0.25–0.65: 1.1 (0.8–1.4); >0.65: 1.4 (1.2–1.7)	Comparison with general population. Healthy worker selection into cohort based on long interval between start of exposure and start of follow-up (left truncation bias)

Kreuzer et al. 2015	German male uranium millers (n=4,054), employed for at least 6 months 1946–1990. Mortality in IHD (ICD10 I20–I25; n=321), and in CVD (I60–I69; n=159)	Coniometric measurements from 1960 and on (n=93,000) were converted to respirable dust and RCS concentrations by parallel sampling reconstructing historical work situations and ventilation. Median RCS exposure was 2.5 (maximum exposure 37 mg/m <sup>3</sup> -ys). Payroll data were linked to estimated exposure by job type and facility.	IHD (mortality; excess RR per cumulative dose of RCS; mg/m <sup>3</sup> -ys): 0.0012 (-0.018 to 0.021), p>0.5 (point estimates as reported by SBU 2017 which were updated as compared to the publication after personal correspondence with M Kreuzer)  CVD (mortality; excess RR per cumulative dose of RCS; mg/m <sup>3</sup> -ys): 0.0035 (-0.025 to 0.032), p>0.5 (point estimates as reported by SBU, see further above)	No data on smoking. The workers were also exposed to radon and gamma-radiation (main focus of the study). This was not adjusted for. Internal analyses (Poisson regression) include deaths 1946–2008, external comparison is limited to deaths 1970–2008.
Gellissen et al. 2019	Nested case-control study within cohort above (Kreuzer et al. 2015). All male. First MI occurring while still employed and at age <65 years; 292 matched (1:3) sets.	Exposure assessment as above, but omitting five years before occurrence of index case. Subdivisions of subjects to reduce bias from pre-hire exposure to RCS. Mean overall cumulative exposure to RCS was 11.5 and 11.3 mg/m <sup>3</sup> -ys in cases and controls, respectively. Tertiles of cumulative exposure: low (reference) <5.74 mg/m <sup>3</sup> -ys, medium 5.74–14.62 mg/m <sup>3</sup> -ys, high ≥14.62 mg/m <sup>3</sup> -ys.	Whole study group: Low tertile OR 1.0 (referent), medium OR 1.65 (1.09–2.51), high OR 1.25 (0.80–1.93). Adjusted for smoking, and erythrocyte sedimentation rate at first medical examination.  Subgroup with presumed least exposure misclassification:  Low tertile OR 1.0 (referent), medium OR 6.53 (1.35–31.5), high OR 6.55 (1.35–31.8). Adjustment as above.	Conditional logistic regression analysis. Additional analyses adjusting for the few cases of metabolic syndrome as a potential mediator yielded similar results.

CI, confidence interval; IHD, Ischemic heart disease; HR, hazard ratio; JEM, job exposure matrix; MI, myocardial infarction; OR, odds ratio; RCS, respirable crystalline silica; SIR, standardized incidence ratio.

Intervals indicated are 95 % CI.

For Björ et al. 2010, 2.5 % RCS corresponds to air levels of approximately >0–0.9 mg/m<sup>3</sup>-ys, >0.9–2.5 mg/m<sup>3</sup>-ys and >2.5 mg/m<sup>3</sup>-ys, in the three exposed categories.

### Early biomarkers of increased cardiovascular risk

There are to our knowledge very few human *in vivo* or animal studies on early biomarkers of CVD in relation to RCS. Most studies have focused on lung toxicity of RCS and evaluated markers for silicosis or markers for cancer-related changes.

In a study of 94 silica-exposed workers (mean years of occupational exposure to silica=31.0) and 35 healthy volunteers, silica exposure was associated with increased plasma concentrations of the pro-inflammatory cytokine IL-6, the adipokine adiponectin, and the immune-related molecules adipsin and resistin ( $p=0.002$ ,  $p=0.034$ ,  $p<0.001$  and  $p=0.048$ , respectively), but not with IL-8 (Sauni et al. 2012).

In a study of 90 tunnel construction workers and 50 referents biomarkers and blood fatty acids were measured before and towards the end of a 12-day work period (Ellingsen et al. 2017). Tunnel construction workers had slightly reduced systemic inflammation and platelet activation although exposed to both  $\alpha$ -quartz and diesel exhaust, which the authors explained by increased physical activity during the exposure period.

In a study of rats exposed to RCS by inhalation (15 mg/m<sup>3</sup>, 6 h/day, 5 days), blood gene expression profiles were determined after latency periods (0–16 weeks). Silica exposure resulted in significantly differentially expressed genes in the blood involved in activation of inflammatory response as the major biological signal (Sellamuthu et al. 2011).

In a study of mice intratracheally exposed (2.5 mg RCS) to silica dust, Guo et al. (2016) showed that inhaled silica induced inflammatory responses in the heart and kidney by elevated mRNA levels of TNF- $\alpha$ , IL-6 and monocyte chemoattractant protein (MCP)-1; and early fibrotic responses in the heart were observed as elevated mRNA levels of collagen I and fibronectin as well as fibrosis of the kidney. Usage of anti-IL-1 $\beta$  mAb decreased the silica-induced inflammatory response of the heart and kidney and also attenuated fibrosis in the mouse kidney.

Other studies have evaluated the cardiovascular toxicity of silica nanoparticles but it is not clear to what extent these nanoparticles are crystalline in nature.

### Research needs

- The few animal and human studies on cardiovascular toxicity performed indicate cardiovascular effects of RCS. However, the mechanisms for cardiovascular toxicity of RCS are unclear. Are the effects direct or indirect via toxicity in the lung? Further studies of dose-response relationships are also needed.
- Gender differences concerning effects exerted by RCS are possible but have only been evaluated in one study (preliminary data only; Wiebert et al. 2017).
- Experimentally fresh RCS surfaces are more cytotoxic than older ones, the implications of this for risk assessment with regard to IHD are unknown.
- The time pattern in risk is not well described. Since RCS is more persistent in the lung one would expect the added risk for IHD also to persist after cessation of exposure (possibly more so than for e.g. welding exposure).

In general, the importance of dose-rate for occupational exposure to small particles is poorly understood. Is the same cumulative dose derived from short-term high-intensity exposure more

or less dangerous with regard to IHD than when it is obtained from long-term low-intensity exposure? Will particles with high persistence in the lung show slower reduction in risk after cessation of exposure than those which are rapidly cleared? How important is the surface activity?

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## Section II: Diesel motor exhaust

Diesel motor exhaust (DME) is a complex mixture of gases and particles formed during combustion in diesel-fuelled motors (Taxell et al. 2016; IARC 2015). Around 80,000 workers in Sweden are estimated to be exposed to DME at the workplace (Kauppinen et al. 2000). DME is generated from diesel-fuelled combustion engines in vehicles, off-road vehicles and equipment, water vessels, and locomotives. In many occupations (e.g. professional drivers), exposure involves exhaust from both diesel- and petrol-fuelled vehicles. Work environments associated solely with exposure to exhausts from petrol-fuelled motors are very rare, and most epidemiological studies are based on exposure circumstances where diesel exhaust is the predominant or only source of exposure. The composition of the exhaust depends fuel quality, motor technology, and systems for after-treatment of exhaust like filters and catalytic converters. Technology has developed considerably over time, reducing the exposure in association especially with passenger cars, but less so for diesel fuelled heavy machines.

DME is associated with health effects both from the respiratory and cardiovascular system. In 2012, the International Agency for Research on Cancer (IARC) classified DME as carcinogenic to humans, based on sufficient evidence for carcinogenicity both in humans and in experimental animals (IARC 2014). In 2017, the SBU reviewed and found moderately strong evidence that occupational exposure to engine exhaust was associated with heart disease (SBU 2017). The review included five cohorts and one case-control study with data on CVD incidence or mortality. The qualitative evidence for a causal association between occupational exposure to motor exhaust and CVD was “moderately strong”, which is the highest level of evidence for observational studies according to the GRADE system used by SBU. It has been estimated that 3.5 % of all MIs in Sweden could be attributed to occupational exposure to motor exhaust (Järholm et al. 2013).

### Epidemiological studies

Boffetta et al. (1988) investigated the association between exposure to DME and CVD in a prospective population cohort study, the American Cancer Society Study. Around 460,000 men were followed 1982–1984. Exposure to DME was assessed from occupational titles and self-assessed, and causes of deaths were obtained from death certificates. Risk ratios were adjusted for smoking and occupational exposure other than DME. The results are shown in Table 4.



Table 4. Associations between exposure to diesel motor exhaust, and risk of cardiovascular disease. Results from Boffetta et al. (1998).

Cause of death	ICD-9 code	No of deaths	Risk ratio
Ischemic heart disease	410–414	398	0.98
Hypertensive heart disease	401–405	21	1.34
Other heart disease	390–398, 415–429	75	0.94
Cerebrovascular disease	430–438	62	1.61*
Arteriosclerosis	440	10	3.12*
Other vascular disease	441–459	15	0.72

\*p<0.05

Risk ratios adjusted for smoking and occupational exposure to asbestos, coal dust, coal tar pitch and gasoline exhaust.

Thus, risks were elevated for cerebrovascular disease and atherosclerosis, but not for IHD in the study by Boffetta et al. (1998). The risk of death from cerebrovascular disease was also investigated stratified by duration of exposure, using a cut-off value for long duration of >15 years. Results are shown in Table 5.

Table 5. Associations between exposure to diesel motor exhaust, assessed by occupational title, and risk of cerebrovascular disease, by duration of exposure. Results from Boffetta et al. (1998).

Duration of exposure, years	Risk ratio for cerebrovascular disease	95 % CI
1–15	1.43	0.89–2.29
>15	1.68	1.06–2.66

CI, confidence interval

Risk ratios adjusted for smoking and occupational exposure to asbestos, coal dust, coal tar pitch and gasoline exhaust.

The mortality from CVD was investigated among 507,000 Finnish men aged 20–64 identified in a census in 1980 and followed until 1994 (Virtanen and Notkola. 2002). Exposure to DME was estimated from a Finnish JEM (FINJEM) applied to occupational titles from the census in 1975 and 1980. Death rates were adjusted for indicators of socioeconomic status. Exposure to DME was associated with a borderline statistically significantly increased mortality from CVD RR 1.06 (95 % CI 1.00–1.14). The RR for cerebrovascular disease was 1.12 (95 % CI 0.97–1.29). Dose-response was investigated for death from MI, but there were no indications of a dose-response trend.

Finkelstein and co-workers (2004) reported a study of unionized construction workers in Ontario, Canada. Membership in the union of operating engineers, operating heavy diesel-

powered machines, was used as a proxy for exposure to DME. The distribution of causes of deaths was compared to the distribution in national death statistics (proportionate mortality ratio, PMR) and to that in other unions of construction workers (Mortality odds ratio, MOR). The study was based on 7,300 deaths, 1,009 of them among heavy equipment operators. There was a non-significantly elevated PMR for IHD in the heavy equipment operators, PMR 1.09 (95% CI 0.96–1.20). The PMR and MOR methods give uncertain and potentially biased risk estimates since they are based on the distribution of causes of deaths and not on absolute risk of death from the studied diagnoses.

The mortality from IHD as well as MI was increased among operating engineers vs. members in other unions of construction workers, as shown in Table 6. The RR were more elevated in younger than in older heavy equipment operators. A larger proportion of non-exposed workers at ages above 65 years may have contributed to this finding.

Table 6. Association between diesel motor exhaust, assessed by occupation\* and death from cardiovascular disease. Results from Finkelstein et al. (2004).

Cause of death	All ages		Ages 25–64		Ages 65+	
	MOR	95 % CI	MOR	95 % CI	MOR	95 % CI
IHD	1.32	1.13–1.55	1.47	1.17–1.84	1.20	0.96–1.55
AMI	1.23	1.00–1.51	1.43	1.07–1.90	1.06	1.00–1.51

\*Membership in union of operating engineers, operating heavy diesel-powered machines. Reference category: membership in other union of construction workers.

CI, confidence interval; MOR, mortality odds ratio; IHD, ischemic heart disease; AMI, Acute myocardial infarction

Torén and co-workers (2007) investigated the health effect of exposure to DME in a cohort including over 175,000 male Swedish construction workers followed 1971–2002. DME exposure was determined by an industry-specific JEM. Exposure to DME was associated with an increased mortality from IHD, RR 1.18 (95 % CI 1.13–1.24), adjusted for smoking habits, BMI and blood pressure at enrolment to study. A small excess risk of cerebrovascular disease was of borderline statistical significance, RR 1.09 (95 % CI 0.99–1.20). No dose-response analysis was reported.

Attfield and co-workers (2012) investigated the mortality in a cohort study of US miners, initiated primarily to investigate the risk of lung cancer from exposure to DME. The cohort included 12,315 workers at eight non-metal mining facilities. Exposure to quartz and radon were sufficiently low not to be potential confounders for lung cancer. Individual historical exposure to respirable elemental carbon (EC) was determined by a measurement program and modelling, although the exposure data were not applied to the analysis of CVD. Standardized mortality ratios (SMRs) were estimated, using US national death rates stratified for sex, race and state as reference. The number of deaths from both IHD and cerebrovascular disease were close to the expected. SMR for IHD was 0.99 (95 % CI 0.91–1.07) and SMR for cerebrovascular disease was 0.89 (95% CI 0.72–1.09). The estimated average exposure to respirable EC, used as a marker of exposure to DME, in the entire cohort was 87.0  $\mu\text{g}/\text{m}^3$  (85.2–88.8) and the exposure to respirable dust was 1.51  $\text{mg}/\text{m}^3$  (1.50–1.53). Subdivision on

underground vs ever over ground workers showed no evidence of an effect of DME on cardiovascular mortality. Exposure-response relations for CVD were not reported.

Laden et al. (2007) reported the cause-specific mortality in a cohort of 54,319 male unionized US trucking industry workers. The cohort was followed from 1985–2000. Group-level adjustment for smoking habits was applied. Analysis of SMR, using US national death rates for reference, showed an increased risk of death from IHD, SMR 1.41 (95% CI 1.33–1.49) (Laden et al. 2007). The risk of cerebrovascular disease was low, SMR 0.69 (95% CI 0.59–0.80).

The risk for death from IHD in relation to job titles and duration of work was later investigated internally in the same cohort by Cox proportional hazards model, adjusting for race, region of residence, company, and residential air pollution (Hart et al. 2013). A special analysis adjusted for the healthy worker survival effect, using information on years on and off work. The results for job titles are shown in Table 7. There was a positive but non-significant trend between work duration and IHD risk.

Table 7. Associations between exposure to diesel motor exhaust, assessed by job title, and risk of death from ischemic heart disease. Data from Hart et al. (2013).

Job title	Adjusted* HR	95 % CI
Long haul driver	1.44	1.22–1.70
Pick-up and delivery driver	1.11	0.96–1.28
Dockworker	1.30	1.12–1.51
Combination	1.11	0.93–1.32
Mechanic	1.10	0.84–1.44
Hostler	1.04	0.79–1.37
Clerk	0.63	0.43–0.91

HR, hazard ratio; CI, confidence interval

\*Adjustments for race, region of residence, company, residential air pollution, and healthy worker survivor effect

The risk of IHD increased, although not statistically significantly, with duration of exposure, also after group-level adjustment for smoking habits.

The exposure to EC and PM<sub>2.5</sub> in the US trucking industry was reported by Davis et al. (2007), as shown in Table 8.

Table 8. Exposure to elemental carbon (EC) and particulate matter (PM)<sub>2.5</sub> by job title. Data from Davis et al. (2007).

Job title	EC, µg/m <sup>3</sup> , arithmetic average	PM <sub>2.5</sub> , µg/m <sup>3</sup> , arithmetic average
Long haul drivers	1.4	52.6
Pick-up and delivery driver	1.6	27.8
Terminal background	0.8	11.9

In conclusion, in the series of studies on the US trucking industry there were indications of an increased risk of IHD in several of the driver groups, and a positive but non-significant dose-response trend in terms of duration of exposure. The levels of EC reported for this industry indicated a considerably lower exposure to DME than among e.g. miners in the US (Attfield 2012).

The risk of first-time MI was investigated in the Stockholm Heart Epidemiology Program (SHEEP), a population-based case-control study from Stockholm, Sweden, by Ilar and co-workers (2014). There were 1,643 cases and 2,235 population controls. Working histories and data on potential confounders were collected by questionnaire and medical examination. Exposure to DME was assessed from a quantitative generic JEM developed for the Stockholm area. ORs were adjusted for sex, age group, hospital catchment area, year of enrolment, smoking habits and alcohol drinking. The results are shown in Table 9. The risk of MI increased with exposure to DME,  $p$  for trend=0.034.

Table 9. Associations between exposure to diesel motor exhaust and risk of MI. Results from Ilar et al. (2014).

Highest exposure to EC for one year, $\mu\text{g}/\text{m}^3$	Average exposure in class, $\mu\text{g EC}/\text{m}^3$ †	Adjusted* OR	95 % CI
Unexposed		1	
>0–21.9	12.6	0.94	0.71–1.25
22.0–42.0	31.6	1.22	0.94–1.59
>42.0	87.5	1.30	0.99–1.71

CI confidence interval; EC, elemental carbon; OR, odds ratio;

\*Adjustments for sex, age group, hospital catchment area, year of enrolment, smoking habits and alcohol drinking.

†Cases and controls combined.

### Cardiovascular disease among professional drivers

There is quite a large number of studies of CVD in professional drivers, especially in bus drivers (Schnall et al. 2000). Many of these studies have demonstrated an excess incidence of IHD or myocardial infarction. This excess has mainly been attributed to three potential causes – exposure to motor exhaust, psychosocial stress, or to a selection of individuals with unhealthy lifestyle to the occupation.

Lewné and co-workers (2007) investigated the exposure to  $\text{PM}_{1.0}$ ,  $\text{PM}_{2.5}$ , EC and  $\text{NO}_2$  (all in  $\mu\text{g}/\text{m}^3$ ) in various occupational groups exposed to motor exhaust, including drivers, in Stockholm, Sweden. The results are shown in Table 10. The exposure to motor exhaust for professional drivers was considerably lower than for tunnel construction workers and lower than for garage workers, regardless of indicator for DME. The average ratio of  $\text{PM}_{1.0}$  to EC was 2.6, and the ratio of  $\text{PM}_{2.5}$  to EC was 3.9.

Table 10. Exposure to specific air pollutants by occupational groups exposed to motor exhaust. Results from Lewné et al. (2007).

Occupational group	PM <sub>1.0</sub>	PM <sub>2.5</sub>	EC	NO <sub>2</sub>
Tunnel construction workers	119	230.6	86.7	350.0
Garage workers – diesel	22.8	41.8	10.7	91.9
Garage workers – petrol	23.6	69.6	11.8	41.6
Construction machine operators	27.6	26.2	7.8	42.7
Outdoor workers exposed to DME	20.7	26.4	4.1	32.2
Bus and lorry drivers	13.5	15.7	6.4	52.9
Taxi drivers	11.3	17.3	6.7	45.4

EC, elemental carbon; NO<sub>2</sub>, nitrogen dioxide; PM<sub>x</sub>, particulate matter with diameter less than x μm

Bigert and co-workers (2003) investigated the potential confounding from life-style habits on the risk of MI in various group of professional drivers, with individual data on life-time working history, smoking, alcohol, hypertension, BMI and diabetes obtained in the population-based case-control study SHEEP. A high risk of MI in the unadjusted analysis was clearly attenuated by adjustment for socioeconomic status, smoking, alcohol, physical inactivity at leisure time, overweight, diabetes and hypertension, as shown in Table 11.

Table 11. Associations between occupation and risk of myocardial infarction. Results from Bigert et al. (2003).

Driver group (driver >1 year)	Crude* OR	95 % CI	Adjusted† OR	95 % CI
Never drivers (reference category)	1		1	
Bus drivers	2.14	1.34–3.41	1.49	0.91–2.45
Taxi drivers	1.88	1.19–2.98	1.34	0.82–2.19
Truck drivers	1.66	1.22–2.26	1.10	0.79–1.53

CI, confidence interval; OR, odds ratio

\*Adjusted for age group and hospital catchment area.

†Adjusted for age group, hospital catchment area, socioeconomic status, smoking, alcohol, physical inactivity at leisure time, overweight, diabetes and hypertension.

The main confounder was a much higher percentage of smokers among the drivers than in the general population.

In conclusion, studies of professional drivers may be less informative about chronic effects of DME on the cardiovascular system from two reasons: (a) Professional drivers of buses, taxi and trucks, are likely to be less exposed to DME than e.g. miners and garage workers (Lewné et al. 2007, Davis et al 2007), and (b) there is a risk for considerable confounding from tobacco smoking habits (Bigert et al. 2003). Thus, studies of professional drivers not adjusting for tobacco smoking may be less informative about effects of DME exposure.

### Early biomarkers of increased cardiovascular risk

Several studies mainly based on controlled exposure or occupational settings have shown associations between exposure to diesel exhaust and early effect biomarkers for CVD. Studies reporting significantly altered early biomarkers of CVD are listed in Table 12 and briefly summarized below.

#### Vascular function and inflammatory markers

Twenty men with stable CHD were exposed to diesel exhaust ( $300 \mu\text{g}/\text{m}^3$ ) or filtered air for 1 hour during periods of rest and moderate exercise. Exposure to diesel was associated with exercise-induced ST-segment depression (Mills et al. 2005).

In a double-blind crossover, controlled study, 27 volunteers (10 healthy and 17 with metabolic syndrome) were exposed to two concentrations of diesel exhausts or filtered air for two hours. Exposure to  $200 \mu\text{g}/\text{m}^3$  was associated with a decrease in brachial artery diameter (0.11 mm; 95 % CI 0.02–0.18), with a smaller but non-significant effect observed at  $100 \mu\text{g}/\text{m}^3$ . There was an increase of endothelin-1 at 200 but not at  $100 \mu\text{g}/\text{m}^3$  of diesel exhaust (Peretz et al. 2008).

Indices of arterial stiffness were investigated in 12 healthy volunteers after exposure to diesel exhaust or filtered air for one hour during moderate exercise. Diesel exhaust exposure induced an increase in augmentation pressure of 2.5 mmHg ( $p=0.02$ ) and an augmentation index of 7.8 % ( $p=0.01$ ), along with a 16 ms reduction in time-to-wave-reflection ( $p=0.03$ ), 10-minutes post-exposure (Lundbäck et al. 2009).

Lucking and co-workers (2011) investigated the effect of exposure to diesel exhaust at a particle mass concentration of  $300 \mu\text{g}/\text{m}^3$  for one hour, with and without a particle filter, in 19 healthy volunteers in a randomized, double-blind, 3-way crossover trial. Diesel exhaust inhalation was associated with reduced vasodilatation and increased *ex vivo* thrombus formation. Inhalation of filtered diesel exhaust elicited no or smaller effects.

The effect of diesel exhaust inhalation was evaluated on circulating blood cell populations, hematological indices, and systemic inflammatory cytokines in a randomized double-blind crossover study of 17 individuals with metabolic syndrome and 15 healthy subjects inhaling filtered air or diesel exhaust (Krishnan et al. 2013). The results suggested that short-term diesel exposure results in hemoconcentration and thrombocytosis, which are determinants of acute cardiovascular events, but no significant effect on cytokines was found.

In a controlled exposure study, 18 healthy volunteers were exposed twice to diluted diesel exhaust ( $\text{PM}_{10} \sim 300 \mu\text{g}/\text{m}^3$ ) and twice to filtered air for 3 h (Xu et al. 2013). Monocyte and total leukocyte counts in peripheral blood were higher after exposure to diesel exhaust than filtered air 20 h post-exposure indicating that diesel exhaust induced inflammatory markers in healthy volunteers. The effects were first seen at 75 min of exposure.

Six healthy volunteers with *GSTM1* null genotype were exposed to diesel exhaust for 2 hours. Exposure to  $300 \mu\text{g}/\text{m}^3$  gave a reduction of baseline brachial artery diameter of borderline statistical significance ( $3.34 \pm 0.27$  mm pre- versus  $3.23 \pm 0.25$  mm post-exposure;  $p=0.08$ ). Decreases were not observed at lower exposure ( $100$  and  $200 \mu\text{g}/\text{m}^3$ ). Exposure to the highest

concentration of diesel also gave an increase of 5 mmHg in diastolic blood pressure as well as a decreased HRV (Tong et al. 2014).

In a study of 90 tunnel construction workers and 50 unexposed controls, biomarkers and fatty acids in blood were measured before and towards the end of a 12 days working period (Ellingsen et al. 2017). Contrary to expectations, tunnel construction workers had slightly reduced systemic inflammation and platelet activation although exposed to both particulate matter,  $\alpha$ -quartz and diesel exhaust, which the authors explained by increased physical activity during the exposure period.

In a study of 54 men highly occupationally exposed to diesel and 55 unexposed male controls in China, plasma levels of 64 immune/inflammatory markers were measured (Bassig et al. 2017). Levels of nine inflammatory markers that were associated with lung cancer risk in a Shanghai study were altered in diesel-exposed workers in the same direction as the lung cancer associations. Among these, associations with the levels of CCL15/MIP-1D were observed in workers exposed to diesel and with increasing EC exposure levels in multivariable linear regression models.

The same Chinese research group carried out repeated personal exposure measurements of PM<sub>2.5</sub> and other diesel engine exhaust constituents in a cross-sectional study of 41 diesel engine testing workers and 46 unexposed controls (Dai et al. 2018). Serum levels of inflammatory biomarkers were compared to unexposed controls, and in the diesel-exposed workers, concentrations of macrophage inflammatory protein MIP-1 $\beta$  were significantly reduced and showed a strong decreasing trend with increasing PM<sub>2.5</sub> concentrations in all subjects as well as in exposed subjects only. Levels of IL-8 and MIP-1 $\beta$  were significantly lower in workers in the highest exposure tertile of PM<sub>2.5</sub> (>397  $\mu\text{g}/\text{m}^3$ ) compared to unexposed controls. Further, significant inverse exposure-response relationships for IL-8 and MCP-1 were also found in relation to increasing PM<sub>2.5</sub> levels among diesel exposed workers.

### Lipids

Diesel engine exhaust has been found to induce lipid peroxidation, a class of oxidative stress, in animal exposure studies. In a human study, Bin and co-workers (2016) evaluated urinary lipid peroxidation biomarkers among 108 workers with exclusive exposure to diesel engine exhaust and 109 non-exposed workers. Results showed that increased levels of lipid peroxidation markers urinary malondialdehyde and 1,N(6)-etheno-2'-deoxyadenosine ( $\epsilon$ dA) were observed in subjects occupationally exposed to diesel engine exhaust. There was a statistically significant relationship between the internal exposure dose (measured as hydroxylated polycyclic aromatic hydrocarbons in urine) and malondialdehyde, 4-hydroxynonenal, and  $\epsilon$ dA. However, it should be noted that both exposure and effect biomarkers were measured in urine and we cannot exclude that the positive associations are due to co-excretion of these biomarkers.

### Platelet activation

Exposure to diesel exhaust may promote atherothrombotic events. In a randomised, cross-over study the effects of acute exposure to diesel exhaust on platelet activation and platelet function was evaluated: 25 healthy men were exposed to ambient and polluted air; 11 of the subjects

also performed exercise during exposure sessions (Wauters et al. 2015). Acute diesel exhaust exposure had no effect on platelet activation at rest, but exercise in polluted air increased the collagen-induced expression of CD62P (P-selectin) and CD63 (dense granule glycoprotein). The increase in the expression of CD62P and CD63 was related to the total amount of PM<sub>2.5</sub> inhaled during the exercise sessions. Platelet aggregation was not impaired after polluted air exposure at rest or during exercise. In conclusion, in healthy subjects, diesel exhaust exposure induced platelet activation as illustrated by a dose-response increase in the release of CD62P and CD63.

### *Epigenetic markers*

Global analysis of circulating miRNAs was performed in an experimental cross-over study of a human population exposed to traffic-related air pollution (Krauskopf et al. 2018). By utilizing next-generation sequencing technology and detailed real-time exposure measurements the authors identified 54 circulating miRNAs to be dose- and pollutant species-dependently associated with PM<sub>10</sub>, PM<sub>2.5</sub>, black carbon, ultrafine particles and NO<sub>2</sub> after 2 h of exposure. The microRNAs may reflect the adverse consequences of traffic pollution-induced toxicity in target tissues including the heart. It should be noted though that the risk for false positives in such a study is rather high.



Table 12. List of studies on exposure to diesel reporting significantly altered early biomarkers of cardiovascular disease.

Reference	Type of study	Diesel dose	Dose-response
Mills et al. 2007	Cross-over study of 20 men with stable coronary heart disease for 1 hour during periods of rest and moderate exercise.	PM 300 $\mu\text{g}/\text{m}^3$	Diesel exposure associated with exercise-induced ST-segment depression.
Peretz et al. 2008	Cross-over study of 27 men and women (10 healthy and 17 with metabolic syndrome), for two hours.	PM <sub>2.5</sub> 101.5 and 205.3 $\mu\text{g}/\text{m}^3$	Exposure to 205.3 $\mu\text{g}/\text{m}^3$ associated with a decrease in brachial artery diameter and an increase of endothelin-1.
Lundbäck et al. 2009	Cross-over study of 12 healthy men with 1 h exposure to diesel during moderate exercise.	PM 350 $\mu\text{g}/\text{m}^3$	Diesel induced an increase in augmentation pressure and augmentation index along with a reduction in time-to-wave-reflection 10 minutes post-exposure.
Lucking et al. 2011	Randomized, double-blind, 3-way crossover trial including 19 healthy volunteers.	PM 300 $\mu\text{g}/\text{m}^3$ for one hour, with and without a particle filter	Diesel exhaust inhalation was associated with reduced vasodilatation and increased ex vivo thrombus formation. Inhalation of filtered diesel exhaust elicited no or smaller effects.
Krishnan et al. 2013	Cross-over study of men and women of exposure to traffic pollution (17 with metabolic syndrome, 15 without) for 2 h.	PM <sub>2.5</sub> 200 $\mu\text{g}/\text{m}^3$	Hematocrit and platelet concentrations increased after diesel exposure. No difference in blood count or systemic inflammatory cytokines.
Xu et al. 2013	Cross-over study of exposure to traffic pollution (18 healthy) for 3 h.	PM <sub>2.5</sub> 300 $\mu\text{g}/\text{m}^3$	Monocyte and total leukocyte counts higher post-exposure.
Tong et al. 2014	6 men and women with <i>GSTM1</i> null exposed for 2 hours.	PM 100.2, 214.4 or 301.5 $\mu\text{g}/\text{m}^3$	Exposure to the 301.5 $\mu\text{g}/\text{m}^3$ gave an increase of 5 mmHg in diastolic blood pressure as well as a decreased heart rate variability.
Wauters et al. 2015	Cross-over study (25 healthy men of which 11 did exercise) for 2 h.	PM <sub>2.5</sub> 300 $\mu\text{g}/\text{m}^3$	Increase in expression of CD62P and CD63 related to the total amount of PM2.5 inhaled during exercise sessions only.
Bin et al. 2016	108 occupationally diesel-exposed and 109 non-exposed workers.	Mean PM <sub>2.5</sub> : 267.45 $\mu\text{g}/\text{m}^3$ in exposed and 91.88 in non-exposed workers; EC 113.69 in exposed and 11.81 $\mu\text{g}/\text{m}^3$ in non-exposed workers.	Lipid peroxidation products in urine (MDA, $\epsilon\text{dA}$ ) showed dose-response relationships with polycyclic aromatic hydrocarbon metabolites in urine.

Ellingsen et al. 2017	90 male tunnel construction workers and 50 male referents before and after 12 days of work.	Mean EC 51 $\mu\text{g}/\text{m}^3$	Lower inflammation and platelet activation in tunnel construction workers after work.
Bassig et al. 2017	54 occupationally exposed and 55 unexposed males.	Mean levels of EC, OC and $\text{PM}_{2.5}$ in the exposed workers were 59.6, 138.9 and 0.4 $\text{mg}/\text{m}^3$ , respectively.	Four immune/inflammatory markers showed association in diesel-exposed workers compared with control workers and an exposure-response relationship with increasing levels of EC was observed for two: CXCL-11/I-TAC was lower and CCL15/MIP-1D was higher across EC exposure groups.
Dai et al. 2018	41 male diesel engine testing workers and 46 male unexposed controls (>60% smokers in each group).	$\text{PM}_{2.5}$ Mean 0.37 $\text{mg}/\text{m}^3$ ; EC 58.1 $\text{mg}/\text{m}^3$ ; OC: 138.1 $\text{mg}/\text{m}^3$	Serum MIP-1b reduced in diesel-exposed workers and showed a decreasing trend with increasing $\text{PM}_{2.5}$ concentrations in all subjects and in exposed subjects only. Clear dose-responses were not found for other inflammatory biomarkers including IL-1, IL-6, IL-8, TNF-a, and MCP-1.
Krauskopf et al. 2018	Cross-over study of walking in Hyde Park and Oxford street for 2 h: non-smoking 24 men and women.	Mean ambient air $\text{NO}_2$ of 7.9 $\mu\text{g}/\text{m}^3$ in Hyde Park versus 18.1 $\mu\text{g}/\text{m}^3$ in Oxford Street. For $\text{PM}_{2.5}$ 5.6 vs 25.6 $\mu\text{g}/\text{m}^3$ ; for BC 1.0 vs 11.4 $\mu\text{g}/\text{m}^3$ ; for $\text{PM}_{10}$ 16.0 vs 37.0 $\mu\text{g}/\text{m}^3$ ; For UFP 5,975 vs 28,656 thousands/ $\text{cm}^3$ .	54 microRNA showed dose-dependent response to all exposure measures. Some of them linked to cardiovascular diseases and inflammation.

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4-HNE, 4-hydroxynonenal; BC, black carbon; EC, elemental carbon; MDA, malondialdehyde; OC, organic carbon; UFP, ultrafine particles

## Conclusions

Epidemiological cohort studies of DME exposed groups of US heavy equipment operators, Swedish construction workers, and US trucking industry workers all indicated an excess risk of CVD in association with exposure to diesel exhaust. No excess risk was noted among US non-metal miners. A US population-based prospective cohort study showed an excess of arteriosclerosis and cerebrovascular disease, but not of IHD, in association with DME exposure. A Swedish population-based case-control study of MI showed an elevated risk of MI in association with exposure to DME, and a quantitative risk assessment was based on exposure estimates from a JEM. An increased risk of MI was found at EC levels around  $90\mu\text{g}/\text{m}^3$ , roughly corresponding to a level of  $350\mu\text{g}/\text{m}^3$  of  $\text{PM}_{2.5}$  ( $90 \times 3.9 = 351$ , based on Lewné et al. 2007).

In occupational and human experimental *in vivo* studies there are dose-response relationships between diesel exposure and early biomarkers of risk of CVD at exposure levels  $\text{PM}_{2.5}$  300–400  $\mu\text{g}/\text{m}^3$ . Analysis of novel epigenetic markers shows associations with exposure markers for diesel exposure down to 25  $\mu\text{g}/\text{m}^3$ . However, their values as predictive markers of CVD are currently unknown.

In conclusion, dose-response data from both epidemiological and human experimental studies indicate negative effects on the cardiovascular system at exposure levels of 300–400  $\mu\text{g PM}_{2.5}/\text{m}^3$ .

### Research needs

Much focus in the scientific literature has been on carcinogenic effects of DME, and the literature on cardiovascular effects is limited. To date, only one epidemiological study of DME exposure addressing cardiovascular risk used quantitative exposure estimates, which can be used for quantitative risk assessment. Further studies with detailed exposure data and individual information on important confounders like tobacco smoking are needed.

The mechanisms behind diesel-induced cardiovascular toxicity are not clear and a more systematic approach evaluating the influence of inflammation, coagulation, lipid peroxidation and epigenetic effects on diesel-related CVD is warranted.

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## Section III: Welding fumes

Welding processes generate both respirable particles and gases. Welders are generally exposed to small particles of iron but also many other particles of metal or non-metal origin (Flynn and Susi 2010). Most of the primary particles in all different welding aerosols have diameters between 5 and 40 nm. Regardless of the welding technique, primary particles have a tendency to form chainlike agglomerates and grow to sizes between 0.1 and 1 µm (Berlinger et al. 2011).

In Sweden the number of welders is approximately 20,000. However, there is about 250,000 workers who weld without categorizing themselves as welders, such as car mechanics and repair workers (Sjögren 2013).

Based on a systematic review of epidemiological studies of occupational exposure to welding fumes SBU (2017) concluded that there is limited evidence for an association with IHD and insufficient evidence for an association with stroke.

In 2017, the IARC classified welding fumes as carcinogenic to humans based on increased risk of lung cancer (IARC 2018).

### Epidemiological studies

An increased mortality from IHD was observed among welders compared with death rates in the general population (Ibfelt 2010, Moulin 1993, Newhouse 1985, Wu 2013). Some cohort studies of welders did not observe any significant differences regarding diseases of the circulatory system (Becker 1999; Milatou-Smith et al. 1997; McMillan and Pethybridge 1983; Puntoni et al. 2001; Simonato et al. 1991; Sjögren 1985; Steenland 2002) and in one study a significantly decreased risk was observed (Beaumont and Weiss 1980).

In Sweden, a series of cohort studies of welders have used successively improved referent cohorts for better comparability. In 1985, male welders were compared with the total male population and the SMR regarding IHD was 0.99 (Sjögren 1985). In 2002, male welders were compared with gainfully employed men and SMR regarding IHD increased 1.06 (95 % CI 1.02–1.11) in a long follow-up (25 years) and to 1.35 (95 % CI 1.10–1.64) in a short follow-up (5 years) (Sjögren et al. 2002). The different risk estimates between these follow-up periods may be explained by a larger proportion of retired and consequently non-exposed welders in the cohort with long-term follow-up. In 2012, welders were compared with manual workers non-exposed to particles. Male and female welders had an increased risk regarding morbidity and mortality due to MI with HRs of 1.19 (95 % CI 1.13–1.25) and 1.29 (95 % CI 1.07–1.56), respectively (Wiebert et al. 2012). This sequence of studies, with improving quality, points in the direction that there is a likely association between welding fume exposure and IHD.

Later studies were better designed and included both fatal and non-fatal cases of disease. In a Danish study, 8,376 male metal workers answered a questionnaire about welding experience and lifestyle. The cohort of 5,866 welders was followed from the start of 1987 until the end of 2006. Information on CVD incidence was retrieved from the Danish National Patient Registry and compared to 5-year age- and calendar year-specific national incidence rates. Increased risks were observed regarding acute MI SIR 1.12, 95 % CI 1.01–1.24), angina pectoris (SIR 1.11,

95 % CI 1.01–1.22) chronic IHD (SIR 1.17, 95 % CI 1.05–1.31) and cerebral infarction (SIR 1.24, 95 % CI 1.06–1.44) (Ibfeld et al. 2010).

#### Meta-analysis

For a meta-analysis, in total 18 studies were identified with estimates of IHD morbidity or mortality among workers exposed to welding fumes. The weighted RR for IHD was 1.09 (95 % CI 1.00–1.19) based on ten study groups. The RR was 1.39 (95 % CI 0.96–2.02) among studies using an internal reference group and 1.08 (95 % CI 0.99–1.18) among studies with an external reference group. Three studies adjusted for smoking and the weighted RR for IHD was 1.14 (95 % CI 0.86–1.53); in seven studied groups adjustment for smoking was not performed (weighted RR for IHD was 1.13, 95 % CI 1.00–1.28). An increased risk was observed for acute MI (RR 1.69, 95 % CI 1.18–2.42) but not for other IHDs (RR 1.06, 95 % CI 0.98–1.14) (Mocevic et al. 2015).

#### Dose-response relationships: epidemiological studies

In a French study of 2,721 welders from 13 factories including 3 shipyards, a relationship was found between duration of employment and mortality from IHD. Employment for 20 years or longer was associated with a significantly increased mortality from IHD, SMR 1.79 ( $p < 0.05$ ) (Moulin et al. 1993).

In the mentioned Danish study (Ibfeld et al. 2010), internal comparisons of the cohort with adjustment for tobacco smoking, alcohol and hypertension medicines showed a tentatively increasing HR for chronic IHD with increasing cumulative exposure to particles. Air samples were collected on filters in the breathing zone behind the welding helmets. The pore size of the filters was 0.8  $\mu\text{m}$ , indicating that smaller particles were not detected by the analysis. The cohort was followed from 1987 to 2006. The mean cumulated estimated particulate exposure was 53.1  $\text{mg}/\text{m}^3\text{-ys}$  all years before baseline (1924–1986) and 8.7  $\text{mg}/\text{m}^3\text{-ys}$  after baseline (1987–2006). A cumulative particulate exposure of 10–50  $\text{mg}/\text{m}^3\text{-ys}$  was associated with an HR of 2.51 (95 % CI 1.15–5.49) for chronic IHD, cumulative exposure of 50–100  $\text{mg}/\text{m}^3\text{-ys}$  was associated with an HR of 2.79 (95 % CI 1.29–6.04) and exposure above 100  $\text{mg}/\text{m}^3\text{-ys}$  was associated with an HR of 1.70 (95 % CI 0.78–3.72) (Table 13, Ibfeld et al. 2010). This possible dose-response relationship must be regarded as tentative due to the low number of cases in the internal reference group and the broken trend at the highest cumulative dose, which may perhaps be explained by the healthy worker survivor effect. A conservative estimate of the lowest dose category of 50  $\text{mg}/\text{m}^3\text{-ys}$  cumulative exposure would correspond to 1.25  $\text{mg}/\text{m}^3$  for 40 years of welding fume exposure.

Table 13. Cumulative exposure to particles and adjusted hazard ratios for cardiovascular disease among 3,499 Danish welders (Table based on figures in Ibfeld et al. 2010).

Cardiovascular disease	Cumulative particulate exposure (mg/m <sup>3</sup> -years)	Number of cases	Hazard ratio (95 % CI)*
Acute myocardial infarction	0–10 (reference)	17	1
	10–50	67	1.11 (0.65–1.89)
	50–100	96	1.43 (0.85–2.41)
	>100	80	1.03 (0.61–1.74)
Angina pectoris	0–10 (reference)	17	1
	10–50	80	1.23 (0.73–2.08)
	50–100	107	1.41 (0.84–2.36)
	>100	95	1.21 (0.72–2.03)
Chronic ischaemic heart disease	0–10 (reference)	7	1
	10–50	61	2.51 (1.15–5.49)
	50–100	83	2.79 (1.29–6.04)
	>100	60	1.70 (0.78–3.72)
Cerebral infarct	0–10 (reference)	7	1
	10–50	32	1.32 (0.58–3.01)
	50–100	32	1.17 (0.52–2.67)
	>100	52	1.54 (0.70–3.39)

CI, confidence interval

\*Adjustments for tobacco smoking, alcohol intake and anti-hypertensive medication.

### Early biomarkers of increased cardiovascular risk

The mechanisms behind cardiovascular toxicity of welding fumes remain to be clarified. Evidence suggests that welding fumes induce chronic inflammation (Kim et al. 2005) and are immunosuppressive. For example, increased susceptibility to pneumococcal pneumonia provides evidence that welding fume exposure can produce immune suppression in humans (Suri et al. 2016; Wong et al. 2010; Marongiu et al. 2016). Seven studies on exposure to welding fumes in relation to early biomarkers of CVD are listed in Table 14.

#### Vascular function and inflammatory markers

Christiani and colleagues have in a series of studies of boilermakers performed repeated measurements of the workers to elucidate the cardiovascular effects of short-term exposure to welding particles (Cavallari et al. 2008; Fang et al. 2009). A few of them are mentioned here. (It should be noted that the frequency of current smoking, another important source for particles and a CVD risk factor, in their studies is rather high: 40–60 %.) In Kim et al. (2005) blood samples were collected from welders (median PM<sub>2.5</sub> 1.69 mg/m<sup>3</sup>) and non-welding controls before and after their work shift. In non-smokers welding fumes were associated with a significant increase in white blood cell and neutrophil counts immediately following exposure and a significant decrease in fibrinogen levels was observed. After welding exposure, CRP levels significantly increased in both non-smokers and smokers. PM<sub>2.5</sub> concentrations were



significantly associated with absolute neutrophil counts in non-smokers, and CRP levels in both non-smokers and smokers (Kim et al. 2005). These data suggest that moderate level of exposure to welding fumes can induce systemic inflammation. Further, in Fang et al. (2010) welding and PM<sub>2.5</sub> exposure were significantly associated with a decrease in circulating adhesion molecules VCAM-1 and an increase in von Willebrand factor in the afternoon after the 6-hour welding. Christiani and co-workers showed that welders had decreased HRV parameters following a 6-hour work shift. Exposure to metal-rich welding fumes across the work shift was associated with decreased HRV parameters (Umukoro et al. 2016a; Fan et al. 2014) and exposure-response relationships between increasing acute work shift PM<sub>2.5</sub> exposure with decreasing acceleration and deceleration capacities of the heart (Umukoro et al. 2016b). Risk of ectopic heart beats, however, was not associated with exposure to welding fumes (Cavallari et al. 2016).

Table 14. List of studies on exposure to welding fumes and early biomarkers of cardiovascular disease.

Reference	Type of study and welding	Welding dose	Dose-response
Kim et al. 2005	Repeated measures of 24 welders and 13 controls.	Median PM <sub>2.5</sub> 1.69 mg/m <sup>3</sup>	In non-smokers, welding fumes associated with a significant increase in white blood cell and neutrophil counts and a significant decrease in fibrinogen levels was observed.
Fang et al. 2010	26 welders 6 h work-shift on a high exposure welding day and/or a low exposure non-welding day.	Median PM <sub>2.5</sub> welding day, 0.39 mg/m <sup>3</sup> and on a non-welding day 0.04 mg/m <sup>3</sup>	Welding and PM <sub>2.5</sub> exposure associated with a decrease in VCAM-1 and an increase in von Willebrand factor in the afternoon after the 6-hour welding.
Ukumoro et al. 2016a	45 welders measured before and after work shift	Mean PM <sub>2.5</sub> during work shift and 0.35 mg/m <sup>3</sup> 0.04 mg/m <sup>3</sup> prior to their work shift.	Exposure-response relationships between increasing work shift PM <sub>2.5</sub> exposure with decreasing acceleration and deceleration capacities of the heart.
Wei et al. 2013	One day exposure two times (non-smoking 11+8; 5 overlapping): mild steel and stainless steel.	Mean PM <sub>2.5</sub> : 74.2 and 114.9 mg/m <sup>3</sup>	Total PM <sub>2.5</sub> exposure associated with a decline in metabolic change of eicosapentaenoic acid N3, docosapentaenoic acid n3, and docosapentaenoic acid n6.
Raulf et al. 2016	190 welders. Stainless steel predominantly.	Median inhalable dust 0.86 mg/m <sup>3</sup>	Dose-response with iron and chromium in the nasal fluid, but not with metals measured in air, and inflammatory and oxidative stress markers.
Li et al. 2015a and 2015b, Xu et al. 2017	Non-smoking welders (n=101) versus controls (n=127), mild steel predominantly.	Welders median 1.2 mg/m <sup>3</sup> respirable dust, controls <0.1 mg/m <sup>3</sup>	Higher blood pressure (BP) and IL-8 in welders compared with controls. Years working as a welder, but not exposure to respirable dust, were significantly associated with increased systolic and diastolic BP. Shorter telomeres was associated with more years working as a welder; higher copy number of mitochondrial DNA was found in welders compared with controls. No association with serum amyloid A, CRP or homocysteine or other inflammatory markers were found.
Dierschke et al. 2017	Chamber study (21 welders; 11 controls): one day welding of mild steel compared with filtered air.	1.0 mg/m <sup>3</sup> respirable dust	Lower exhaled breath leukotriene B4 after welding exposure, increased IL6 and decreased IL-8 compared with filtered air. No association with inflammatory cells.

Studies examining gene expression have begun to reveal the mechanisms by which exposure affects welders. Welding fume- (median PM<sub>2.5</sub> 2.44 mg/m<sup>3</sup>) induced alterations in gene expression in whole blood were found for genes involved in the inflammatory response, including pro-inflammatory mediators, cytokine receptors, downstream signal transduction genes, and cytotoxic granulysin (Wang et al. 2005). A follow-up study using a similar population (median PM<sub>2.5</sub>: 0.948 mg/m<sup>3</sup>) extended these observations into a post-exposure period. Some acute welding fume-induced effects on gene expression profiling were transient in non-smoking welders, with most diminishing the following day (Wang et al. 2008). Further, in a recent study on German welders (median inhalable dust concentration, 0.86 mg/m<sup>3</sup>) an immune response but also metalloproteinase (MMP9, TIMP1) protein levels, and the leukotriene B4 in nasal lavage were altered in relation to work-shift exposure to Chromium, Nickel and to some extent to Iron (Raulf et al. 2016). In contrast, in a cross-sectional study of Swedish welders (median 1.1 mg/m<sup>3</sup> respirable dust) and controls there was limited evidence for increased inflammation, by measuring cytokines and CRP, in relation to welding fumes exposure but higher blood pressure (Li et al. 2015a). Also in a Swedish chamber study with one-day welding exposure (1.0 mg/m<sup>3</sup> respirable dust), there was little evidence for an immune response but exhaled leukotriene B4 was clearly elevated in welders with symptoms (Dierschke et al. 2017). The role of inflammation in CVD of welding fumes is unclear and studies suggest that a low-to-moderate exposure to welding fumes may affect the cardiovascular system by other mechanisms, maybe as a direct particle effect, without preceding inflammation.

### Lipids

A recent study also indicates effects of welding fumes on unsaturated fatty acids which may have implications for risk of CVD. Wei et al. (2013) performed a two-stage, self-controlled exploratory study including boilermakers from a discovery panel (n=11) and boilermaker welders (n=8) using electric arc and MIG welding from a validation panel. Eicosapentaenoic or docosapentaenoic acid metabolic changes post-welding were significantly associated with particulate (PM<sub>2.5</sub>) exposure (p<0.05). The combined analysis by linear mixed-effects model showed that exposure was associated with a statistically significant decline in eicosapentaenoic acid, docosapentaenoic acid and docosapentaenoic acid, indicating that exposure to metal welding fumes decreases unsaturated fatty acids with an exposure-response relationship.

### DNA damage and epigenetic markers

In the welders mentioned above, shorter telomeres (a marker for CVD; Haycock et al. 2014) and slightly elevated oxidative DNA damage compared with the controls were observed (Li et al. 2015b; Xu et al. 2017). Further, the welders had significantly reduced DNA methylation levels (hypomethylation) of the *F2RL3* gene, which encodes a protein involved in blood coagulation, compared with controls (Hossain et al. 2015). *F2RL3* is implicated in blood coagulation and hypomethylation of *F2RL3* is a risk marker for CVD and CVD prognosis (Zhang et al. 2014; Breitling 2013).

## Conclusions

Epidemiological studies of welding fumes, with unbiased control groups, have found increased risks regarding CVD, and a meta-analysis has shown a significantly increased risk of IHD. One study found a significantly increased IHD mortality after 20 years of employment. Another study observed tentatively increasing risks of IHD with increasing cumulative particle exposure. Based on this study, the tentative critical respirable welding fume concentration regarding IHD is around  $1.0 \text{ mg/m}^3$ . Studies on early biomarkers of CVD suggest inflammatory responses to welding fumes at respirable dust levels around  $1.0 \text{ mg/m}^3$  as well as effects on blood pressure and non-inflammatory changes related to future risk of CVD. Thus, both epidemiological and human experimental data suggest that exposure to respirable particles from welding down to about  $1 \text{ mg/m}^3$  is harmful to the cardiovascular system.

## Research needs

There is need for well-designed dose-response studies for welding fume in general but also for specific types of welding fume such as fume from zinc-coated steel. Further, it is not clear if it is all or one of three general pathways by which welding particles may affect the cardiovascular system: eliciting a systemic proinflammatory response, alteration in systemic autonomic nervous system balance or through transmission of particles directly into the circulation.

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## 9. Noise

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The evidence on biological effects of noise is provided by laboratory studies, field investigations and epidemiological research. Acute effects such as hearing loss or tinnitus occur if the sound level is high. Effects of long-term exposure to more moderate levels of noise may develop over years of exposure. Long-term exposure to noise from road traffic, railways and aircraft has been studied in relation to CVDs primarily during the last two decades. The epidemiological evidence was evaluated in a recent systematic review by van Kempen et al. (2018), performed within the framework of the development of new WHO Environmental Noise Guidelines for the European Region. Göran Pershagen was member of the Guideline Development Group for the WHO Guidelines as well as coauthor of the systematic review on cardiovascular and metabolic effects of environmental noise.

This chapter initially summarizes the evidence on cardiovascular effects of transportation noise, primarily in relation to hypertension, IHD and stroke. Possible effects by noise on risk factors for CVD are also taken up, where most of the evidence exists for T2DM and obesity. Furthermore, interactions of relevance for the risk assessment are highlighted. Cardiovascular effects of noise exposure in the work environment are described separately. Finally, a section covers possible mechanisms behind the effects by noise on the cardiovascular system.

### Hypertension

The majority of available publications on transportation noise and hypertension are of cross-sectional design. The first longitudinal study on hypertension in relation to transportation noise was performed by Eriksson et al. (2007). A subsequent report based on the same cohort showed a tendency to a positive association for the incidence of hypertension in relation to aircraft noise for men, with a relative risk (RR) of 1.17 and a 95 % CI of 0.90–1.51, but not for women, RR 0.85 (95 % CI 0.62–1.15) *per* 10 dB  $L_{den}$  (Eriksson et al. 2010). Using enhanced methodologies for exposure and outcome assessments an increased HR was observed for both sexes combined (HR 1.16, 95 % CI 1.08–1.24) *per* 10 dB  $L_{den}$  (Pyko et al. 2018). Aggregated data from nine cross-sectional studies on aircraft noise tended to show an association with hypertension (RR 1.05; 95 % CI 0.95–1.17) *per* 10 dB  $L_{den}$  (van Kempen et al. 2018). A recent cohort study from Greece reported that nighttime aircraft noise was associated with incident hypertension with an OR of 2.63 (95 % CI 1.21–5.71) *per* 10 dB  $L_{night}$  (Dimakopoulou et al. 2017).

The WHO review found a statistically significant association between road traffic noise and hypertension prevalence with a RR of 1.05 and 95 % CI of 1.02–1.08 *per* 10 dB  $L_{den}$  based on a meta-analysis of 26 cross-sectional studies (van Kempen et al. 2018). This was, however, not confirmed in a cohort study from Denmark, reporting an incidence rate ratio (IRR) of 0.97 (95 % CI 0.90–1.05) *per* 10 dB  $L_{den}$  (Sørensen et al. 2011b). In a combined analysis of several European studies road traffic noise tended to be weakly associated with the incidence of self-reported hypertension but not with measured hypertension showing RRs of 1.03 (95 % CI 0.99–1.07) and 0.99 (95 % CI 0.94–1.04) *per* 10 dB  $L_{den}$ , respectively (Fuks et al. 2017). Furthermore,



there was no increased risk of hypertension related to road traffic noise exposure in a recent study by Pyko et al. (2018), with a HR of 0.93 (95 % CI 0.86–1.10) *per* 10 dB  $L_{den}$ .

For railway noise, the WHO review included four cross-sectional investigations, together showing a tendency to an association with prevalence of hypertension, RR 1.05 (95% CI 0.88–1.26). Furthermore, a longitudinal study by Sørensen et al. (2011b) suggested a positive association for incidence of hypertension with an incidence rate ratio (IRR) of 1.08 (95 % CI 0.98–1.19) in those exposed to railway noise of 60 dB  $L_{den}$  or more. The cohort study by Pyko et al. (2018) showed a HR of 0.91 (95 % CI 0.82–1.02) *per* 10 dB  $L_{den}$  of exposure to railway noise.

Summing up, the WHO review rated the quality of the evidence on transportation noise and hypertension as “very low” (van Kempen et al. 2018). This primarily had to do with the fact that mostly cross-sectional studies were available with well-known limitations regarding possibilities for causal inference. Later published data from longitudinal studies suggest that an increased risk of hypertension may result from long-term exposure to aircraft noise.

### Ischemic heart disease and stroke

Over last decades there is growing evidence of adverse cardiovascular effects of transportation noise from different sources based on studies of prevalence, incidence as well as mortality from IHD and stroke. Regarding road traffic noise the WHO review included results from three cohort and four case-control studies, and reported a statistically significant association for incidence of IHD with a RR of 1.08 (95% CI 1.01–1.15) *per* 10 dB  $L_{den}$  (van Kempen et al. 2018). Moreover, a visualisation of the shape of the association indicated that the risk of IHD increases continuously from around 50 dB  $L_{den}$ . Overall, the quality of the evidence for road traffic noise and incidence of IHD was rated as “high”.

For aircraft noise and incidence of IHD, the review calculated a RR of 1.09 (95 % CI 1.04–1.15) *per* 10 dB  $L_{den}$  based on two studies with ecological design. Considering railway noise, the review included four cross-sectional studies with a pooled RR of 1.18 (95 % CI 0.82–1.68) *per* 10 dB  $L_{den}$  for the prevalence of IHD. The quality of the evidence was rated as “very low” (van Kempen et al. 2018).

The WHO review suggested an association of transportation noise with IHD mortality and reported RR estimates for aircraft and road traffic noise of 1.04 (95 % CI 0.98–1.11) and 1.05 (95 % CI 0.97–1.13) *per* 10 dB  $L_{den}$ , respectively. Moreover, a recent nationwide cohort study from Switzerland found a statistically significant association for all three transportation noise sources and MI mortality with adjusted HR *per* 10 dB  $L_{den}$  of 1.038 (95 % CI 1.019–1.058), 1.018 (95 % CI 1.004–1.031), and 1.026 (95 % CI 1.004–1.048) from road traffic, aircraft and railways, respectively (Héritier et al. 2017).

Relatively few studies investigated the impact of transportation noise on stroke. One cohort study showed a RR for stroke incidence related to road traffic noise exposure of 1.14 (95 % CI 1.03–1.25) *per* 10 dB  $L_{den}$  (Sørensen et al. 2011a). With regard to aircraft noise, the WHO review included two ecological studies with combined RRs of 1.05 (95 % CI 0.96–1.15) *per* 10 dB  $L_{den}$  for stroke incidence and 1.07 (95 % CI 0.98–1.17) *per* 10 dB  $L_{den}$  for stroke mortality (van

Kempen et al. 2018). Overall, The WHO systematic review rated the quality of the evidence supporting an association between transportation noise and stroke as “low”.

In the thesis by Pyko (2018) no clear or consistent associations were observed between transportation noise exposure and risk of IHD or stroke. However, there appeared to be an increased risk of IHD in women related to road traffic noise exposure, while the opposite held true for men. The overall result appears comparable to a recent Swedish cohort study on MI and road traffic noise showing a RR of 0.99 (95 % CI 0.86–1.14) *per* 10 dB  $L_{den}$  (Bodin et al. 2016).

It may be concluded that the evidence points to an increased risk of IHD related to long-term exposure to noise from road traffic, although this is not confirmed by recent Swedish data. The absence of associations may have to do with lower exposure to noise. For other cardiovascular outcomes very few longitudinal studies are available on the possible role of exposure to transportation noise.

### Type 2 diabetes

Seven studies on noise and T2DM were evaluated in the WHO review, mostly of cross-sectional design (van Kempen et al. 2018). The quality of the evidence supporting an association between traffic noise and diabetes was rated as “low”. Only few cohort studies have assessed the relation between environmental noise exposure and T2DM. In general, positive associations were found (Eriksson et al. 2014, Sørensen et al. 2013, Clark et al. 2017, Eze et al. 2017). Most studies focused on road traffic noise, however, suggestive associations have been observed for aircraft noise (Eze et al. 2017) but not for railway noise (Eze et al. 2017, Roswall et al. 2018). Overall, a role of transportation noise for development of T2DM is suggested but the evidence is not conclusive.

### Obesity

The first study of a longitudinal design on obesity in relation to transportation noise showed an association between aircraft noise exposure and waist circumference with an increment of 1.51 cm and 95 % CI of 1.13–1.89 *per* 5 dB  $L_{den}$ , however, no clear associations were reported for other markers like body mass index (BMI) (Eriksson et al. 2014). In a later analysis of the same cohort but with more detailed exposure assessment a 10 dB  $L_{den}$  increase in aircraft noise exposure was associated with a waist circumference increase and weight gain of 0.16 cm/year (95 % CI 0.14–0.17) and 0.03 kg/year (95 % CI 0.01–0.04), respectively (Pyko et al. 2017).

Recent studies have provided inconsistent results on road traffic noise exposure and obesity markers. A cross-sectional Norwegian study did not find an association between road traffic noise exposure and BMI with estimates of 0.01 (95 % CI -0.11–0.13) and -0.04 (95 % CI -0.14–0.06) kg/m<sup>2</sup> *per* 10 dB  $L_{den}$  in women and men, respectively (Ofstedal et al. 2015). The only statistically significant positive association was seen in women who reported that they were highly noise sensitive. A cross-sectional study from Denmark reported associations between road traffic noise 5 years preceding the enrolment and BMI as well as waist circumference with estimates of 0.19 kg/m<sup>2</sup> (95 % CI 0.13–0.24) and 0.30 cm (95 % CI 0.16–0.45) *per* 10 dB  $L_{den}$ ,

respectively (Christensen et al. 2016). The findings were confirmed in a longitudinal study of the same cohort with road traffic being associated with yearly weight gain of 15.4 g (95 % CI 2.14–28.7) and a yearly waist circumference increase of 0.22 mm (95 % CI 0.02–0.43) *per* 10 dB  $L_{den}$  during a mean follow-up time of 5 years (Christensen et al. 2015). We found a statistically significant increase in waist circumference of 0.04 cm/year (95 % CI 0.02–0.06) *per* 10 dB  $L_{den}$  of exposure to road traffic noise, but no association to weight gain, in a recent cohort study (Pyko et al. 2017).

Considering railway noise, a cross-sectional Danish study found statistically significant associations of 0.18 kg/m<sup>2</sup> (95 % CI 0.00–0.36) for BMI and 0.62 cm (95 % CI 0.14–1.09) for waist circumference in those exposed to rail traffic noise at levels above 60 dB  $L_{den}$  (Christensen et al. 2016). A longitudinal study from the same team reported estimates for weight gain and waist circumference change in relation to railway noise of 3.57 g/year (95 % CI -6.07–13.2) and of -0.065 mm/year (95 % CI -0.22–0.093) *per* 10 dB  $L_{den}$ , respectively (Christensen et al. 2015). No clear association between railway noise exposure and waist circumference increase or weight gain was noted in a recent Swedish cohort study (Pyko et al. 2017).

Overall, some findings suggest that transportation noise exposure may be associated with obesity markers, however, the WHO review rated the quality of the evidence as “low” (van Kempen et al. 2018). Results from a recent Swedish study has strengthened the support for a causal role of exposure to particularly aircraft and road traffic noise.

### Interactions

Transportation noise exposure is one among many environmental stressors that may cause adverse health effects. According to the multiple environmental stressor theory, several stressors may enhance the effect of each other (Stansfeld and Matheson 2003). Thus, based on data from the SHEEP study, Selander et al. (2013) found that exposure to a combination of traffic noise, occupational noise and job strain was particularly harmful. Participants exposed to one, two, or three of these factors showed increasing risks of MI with ORs of 1.16, (95 % CI 0.97–1.40), 1.57 (95 % CI 1.24–1.98) and 2.27 (95 % CI 1.41–3.64), respectively. Moreover, simultaneous exposure to two or three of these factors was common and occurred among about 20 % of the controls.

In most epidemiological studies on health risks related to noise exposure effects of combined exposure to different noise sources were not investigated. However, results from a Danish study suggested a stronger association between road traffic noise and weight gain as well as waist circumference increase in those simultaneously exposed to railway noise >55 dB  $L_{den}$  (Christensen et al. 2015). Pyko et al. (2017) found that the IRR of central obesity in relation to exposure to different transportation noise sources (road traffic, railway and/or aircraft noise) increased from 1.22 (95 % CI 1.08–1.39) among those exposed to only one source to 2.26 (95 % CI 1.55–3.29) among those exposed to all three transportation noise sources at levels of 45 dB  $L_{den}$  or more. Higher risks appeared of both IHD and stroke incidence in those exposed to all three noise sources simultaneously, with a HR of 1.57 (95 % CI 1.06–2.32) and 1.42 (95 % CI 0.87–2.32), respectively (Pyko et al. 2019).

Several epidemiological studies have reported an interaction between transportation noise exposure and age. Studies on hypertension by Bodin et al. (2009) and de Kluizenaar et al. (2007) showed stronger associations for road traffic noise among middle-aged (40–60 years) than at higher ages. However, cohort studies focused on stroke and T2DM indicated stronger effects in those over 60 and 64 years of age, respectively (Sørensen et al. 2011a and 2014). Available studies on obesity in relation to transportation noise did not report age interactions (Christensen et al. 2015 and 2016, Oftedal et al. 2015).

The evidence on gender interaction in noise studies appears inconsistent. Thus, Eriksson et al. (2010) reported a significantly increased risk of hypertension in relation to aircraft noise exposure increase of 5 dB  $L_{den}$  in men, but not in women. Babisch et al. (2005) found that road traffic exposure  $>70$  dB  $L_{day(6-22)}$  was associated with MI only in men. Results of a Danish cohort study on MI also suggested stronger effects in men (Sørensen et al. 2012). Huss et al. (2010) reported increased risks of MI mortality related to aircraft noise in men but not in women. However, Selander et al. (2009b) and Beelen et al. (2009) did not find gender differences in cardiovascular incidence and mortality related to road traffic noise. Moreover, Gan et al. (2012) reported no gender differences but found a 7 % non-significant excess risk of coronary mortality in women after adjustment for traffic-related air pollutants. A gender difference in IHD risk related to road traffic and aircraft noise exposure was found by Pyko et al. (2019), with higher risks indicated in women.

There is conclusive evidence that long-term exposure to air pollution such as airborne particle can increase the risk of CVD (WHO 2016). However, it is not common in noise studies to have measures of air pollution or address the issue of co-exposure to noise in air pollution studies, although the two exposure factors may have important common sources, such as road traffic. Selander et al. (2009b) investigated the possible modification of the association between road traffic noise and incidence of MI by air pollution but no strong interaction was revealed.

### Cardiovascular effects of noise in the work environment

Health effects of noise in the work environment has been extensively studied, and there is a huge scientific literature on noise induced hearing loss in industrial environments. Non-auditory effects of occupational noise are attracting increasing attention, especially the effects on the circulatory system (Basner et al. 2014). An early and extensive review by Kristensen (1989) identified 37 studies regarding occupational noise and cardiovascular disease published after 1980. Many studies were of questionable quality, using a cross-sectional design or rough surrogates of exposure, but the authors considered the results from this review to give “reasonable support” for a causal association between exposure to noise and CVD, mainly based on observations of elevated blood pressure in association with occupational exposure to noise.

A meta-analysis published in 2002 (van Kempen et al. 2002) identified 14 studies published after 1989, mainly of cross-sectional character, regarding occupational noise and blood pressure. The pooled estimate of the elevation in systolic blood pressure per 5 dB(A) of exposure was 0.51 mmHg (95 % CI 0.01–1.00). Thus, the effect was small but statistically significant. There was a large heterogeneity in findings between studies. The same meta-analysis identified 9 studies on occupational noise and chronic hypertension. The findings were inconsistent but the

pooled estimate from a random effects model showed a pooled RR estimate for hypertension per 5 dB(A) increase in exposure of 1.14 (95 % CI 1.01–1.29).

A recent systematic review and meta-analysis focussed on prospective cohort studies published after 2000 (Skogstad et al. 2016a, Skogstad et al. 2016b). Three studies investigated the association between objectively assessed exposure to noise and the risk of developing hypertensive disease. Occupational exposure to noise >85 dBA was associated with an increased risk of a diagnosis of hypertension in all three studies. The summary HR was 1.38, which was of borderline statistical significance (95 % CI 1.01–1.87). A fourth prospective study included in the review found a positive association between occupational noise levels and measured blood pressure.

The same review (Skogstad et al. 2016a, Skogstad et al. 2016b) identified five prospective studies on the mortality from CVD. Several of the studies used self-reported data on exposure. The meta-analysis showed a pooled HR of 1.12 (95 % CI 1.02–1.24), and there was no significant heterogeneity between studies ( $p > 0.05$ ). One of the larger studies was of special interest. It was based on over 27,000 Canadian lumber-mill workers, using dosimeter-based exposure assessment and information on causes of deaths from national records. An analysis of SMR showed a small or non-existent risk excess for CVD mortality in association with noise exposure. A subgroup analysis of those who had not used hearing protection devices showed a statistically significant positive dose-response relationship with increasing duration of exposure, regardless if a cut-off of 85, 90 or 95 dBA was used to define exposure (Davies et al. 2005).

In the same review, there were three studies investigating the relationship between occupational exposure to noise and self-reported or hospital-verified diagnoses of CVD. The pooled RR was 1.34 (95 % CI 1.15–1.56). However, it is possible that two of these studies (Virkkunen 2005 and Virkkunen 2006) at least partly was based on the same study base (the Helsinki Heart Study), and should not be considered to contribute to the meta-analysis more than once. It is not likely that this would change the main conclusion, though.

The SBU has recently evaluated the strength of evidence for an association between various occupational exposures, including noise, and development of CVD (SBU 2015). The review, which did not include cross-sectional studies, included the longitudinal studies reviewed by Skogstad et al., but also identified some additional studies of relevance. In all, 13 studies were reviewed, of which six were from the Nordic countries, two from the rest of Europe, four from North America and one from Asia. Nine of the studies concerned heart disease (MI or IHD), two concerned CVD in general and two concerned stroke. The evidence was classified as limited (grade 2 in a 4-point grading system) for an association with CVD, heart disease as well as with stroke.

In summary: There is strong evidence that occupational exposure to noise is associated with an elevated blood pressure, and there is moderately strong evidence that long-term exposure to occupational noise is associated with an increased prevalence of hypertension. There is a limited number of epidemiological studies of long-term exposure to occupational noise and CVD. Several of these studies show a small or modest increase in risk of CVD in association with occupational noise, although findings are not consistent and data do not allow firm conclusions about dose-response relationships. Taken together, an association between exposure to occupational noise and development of cardiovascular disease is credible. There is evidence for

an association with both IHD and stroke. Dose-response is insufficiently studied, but most occupational studies are from environments where noise levels may induce hearing loss (>85 dBA). More research is needed to investigate mechanisms and dose-response.

### Biological mechanisms of noise effects

According to the general stress model, noise can cause metabolic and cardiovascular effects through the indirect pathway, i.e. subconsciously activate the sympathetic nervous system as well as the endocrine system lowering quality of sleep, communication, and activities, with subsequent emotional and cognitive responses and annoyance (Babisch 2003).

The auditory system is as an important warning system, which remains active also during sleep. Noise-induced effects are generally realized through two different systems, the Sympathetic-Adrenal-Medullary (SAM) axis and the Hypothalamic-Pituitary-Adrenal (HPA) axis (Lundberg 1999; Spreng 2000a). The SAM axis describes how the body prepares for “fight-or-flight” with mobilisation of energy to the muscles, heart and brain, and reduction of blood flow to the internal organs by secretion of adrenaline and noradrenaline from the adrenal medulla. Effects of adrenaline and noradrenaline include increased heart rate, stroke volume and vasoconstriction (resulting in increased blood pressure), mobilisation of glucose and free fatty acids as well as aggregation of thrombocytes (Babisch 2003).

The HPA axis is responsible for an endocrine response with production of glucocorticoids, including cortisol (Majzoub 2006). Effects of cortisol include elevation of blood glucose levels, lipolysis, suppression of immune responses and elevations of blood pressure (Babisch 2003; Spreng 2000b). Hyperactivity of the HPA axis, commonly seen in chronic stress situations, is characterised by a “defeat-type” of reaction and is associated with feelings of distress, anxiety and depression (Björntorp 1997; Martinac et al. 2014). Chronically high levels of cortisol may lead to several health effects including alterations in the adipose tissue and visceral fat deposition, hypertension, dyslipidemia and insulin resistance (Björntorp 1997; Eriksson et al. 2010 and 2014; Kyrou and Tsigos 2007; Rosmond 2003; Selander et al. 2009a; Spreng 2000b).

Transportation noise effects on cardiovascular or metabolic functions may also be mediated through sleep disturbances. Normally sleep has a restorative effect with reduced heart rate and blood pressure, as well as decreased brain glucose metabolism. This effect is achieved by inhibited activity of the HPA axis and the sympathetic nervous system as well as a release of anabolic growth hormones (van Cauter et al. 2008). If transportation noise exposure persists over an extended period of time a chronic noise-induced sleep disturbance may arise (Muzet 2007; Pirrera et al. 2010). Thus, long-term evening and night-noise exposure may be of greater importance than daytime exposure. Miedema and Vos (2007) showed clear exposure-response associations between night-time noise and self-reported sleep disturbance. Aircraft noise is associated with more sleep disturbances than road traffic, followed by railway noise at comparable noise levels. However, road traffic is the most common source of transportation noise and contributes to more sleep disturbances in the general population than aircraft or railway noise.

Sleep-deprivation may be of importance for the development of metabolic changes by effects on the carbohydrate metabolism and appetite regulation. Studies have shown associations between



sleep-restriction and impaired glucose tolerance, decreased insulin sensitivity as well as increased risk of T2DM (Spiegel et al. 1999; Cappuccio et al. 2010). The two hormones ghrelin and leptin are regulators of food intake and exert opposing functions on appetite and energy expenditure. Disturbance of sleep may affect the balance of these hormones by reducing leptin and increasing ghrelin, subsequently leading to increased adiposity and BMI (Chaput et al. 2007; Taheri et al. 2004).

## Conclusions

Environmental exposure to transportation noise has been associated with several cardiovascular outcomes, primarily hypertension, IHD and stroke. The most consistent evidence relates to long-term exposure to road traffic noise and IHD. Furthermore, recent studies suggest that transportation noise increases the risk of obesity and T2DM, both important risk factors for CVD. Studies on occupational noise exposure provide some support for increased risks of CVD. Given the well-known effects by noise in causing stress responses and sleep disturbances, which are associated with both cardiovascular and metabolic outcomes, it appears plausible that noise exposure can increase the risk of cardiovascular disease.

## Research needs

- High quality studies are needed on development of IHD and stroke in relation to noise exposure from different transportation sources (roads, railways and aircraft) as well as in the work environment.
- Studies on obesity and T2DM are important for assessing the overall health impact by noise exposure as well as for the understanding of aetiological pathways behind the associations with CVD.
- There is a great need for studies on interactions between environmental stressors (noise from different transportation sources, noise in the workplace, occupational stress etc.) in relation to the risk of CVD.
- In particular, the number of studies on interactions between air pollution and noise exposure is very limited, although both these factors have been related to CVD and exposures often occur together.
- Noise in the work environment is associated with increased blood pressure, but the association with development of chronic hypertension and CVD is not well established. More studies are needed regarding the causal association between occupational noise and development of CVD, as well as on dose-response relationships.

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## 10. Conclusions and future research needs (English and Swedish version)

In the present report, researchers at IMM active in different CVD related research areas, summarize evidence from epidemiological as well as experimental mechanistic studies concerning the influence from environmental risk factors on the development of CVD. On top of the established cardiovascular risk factors (summarized in Chapter 1), several environmental factors including occupational exposures seem to have important roles and are at the same time preventable. For some factors, such as air pollution, as shown in the present report, the evidence for causality behind observations observed is strong, whereas for other factors the available scientific evidence of contribution to CVD risk is weaker. A common denominator for many of the environmental factors observed to be associated with risk of CVD, is a suggested effect on inflammation and atherosclerosis. The scientific evidence for such effect is accumulating for several environmental exposures, including specific components of air pollution, noise, certain metals and arsenic.

The role of diet in CVD aetiology is undoubtedly important. Briefly, according to consistent scientific evidence, dietary habits that reduce cardiovascular risk are characterized by a high intake of fruit, vegetables and whole grain and a reduced intake of sugar, salt and processed meat. Dietary supplements seem not to reduce cardiovascular risk. The lion's share of the epidemiological studies on nutritional influences on CVD are observational, which may be a limitation as discussed in Chapter 3. More intervention studies are needed to corroborate findings from observational data. Continued research on biological mechanisms that may underly the observed associations is also warranted. Inflammation is increasingly discussed as a potential biological pathway through which diet affects cardiovascular health. Future research should also address the role of the microbiome.

Exposure to POPs, mainly via food, have been associated with increased CVD risk, through effects on e.g. blood pressure and lipid metabolism. However, the scientific evidence for a causal role in CVD is weak. Considering that POPs are spread in the environment and accumulate in living organisms, there is a need to increase knowledge concerning their potential role in atherosclerosis and CVD. Possible mixture effects should also be addressed.

Air pollution is a unifying concept for gases and airborne particles that may negatively affect human health and environment. Out of the individual pollutants, the scientific evidence for adverse cardiovascular effects is particularly strong for the inhalation of fine particulate matter. Both short- and long-term exposures represent important hazards. A connection between air pollution and AF has repeatedly been observed, but more research is needed to corroborate findings and to elucidate aetiological pathways.

The research literature on urban greenness points at beneficial effects on cardiovascular health. Several potential underlying reasons for such effects have been suggested, including that greenness in the residential environment may have stress-reducing effects and promote recreational walking and other physical activity. However, a challenge for studies in this area is to take into account potential confounding factors such as socio-demographic factors. Further studies that use prospective study design and individual-level data are needed to clarify the role of urban greenness on cardiovascular health. Despite a relatively weak state of knowledge, it

seems relevant for city planners to consider potential cardiovascular health benefits from urban greenness.

There is strong evidence that high temperature increases risk of cardiovascular mortality. Such association may however show regional variations depending on varying heat sensitivity; adaptation measures may differ by region, and populations may have varying coping capacity. Future research should address such issues. In addition to cardiovascular mortality, increased knowledge about associations with cardiovascular morbidity is needed.

The three occupational exposures considered in the present report – RCS, DME and welding fumes – have all been found associated with adverse effects on the cardiovascular system. However, more studies are needed to corroborate findings and to evaluate dose-response relations. The studies on RCS exposure have repeatedly shown association with increased risk of MI even at low exposure levels. Thus, this exposure should be kept as low as possible. RCS occurs as a component of the dust, e.g. in mining as a component of dust from the rock, or in construction as part of concrete dust. Caution concerning DME exposure and welding fumes is also important, considering they are associated with harmful effects in epidemiological as well as human experimental studies.

Long-term exposure to traffic noise is associated with increased risk of CHD. Exposure to noise in the work environment is associated with acute elevation of blood pressure but the risk of chronic hypertension and CVD is less well established. More studies are needed to investigate causality as well as dose-response. Plausible biological mechanisms behind a causal relation between noise and increased risk of CVD are those of general stress models and include effects on the sympathetic nervous system and the endocrine system. Because noise from transportation often co-occurs with air pollution, it is a challenge to elucidate their individual effects. Further research should also address potential interactions between environmental stressors, such as noise and air pollution.

For most factors considered in the present report, the evidence is stronger for certain CVD diagnoses than others. This relates to that the research literature tends to focus on the more common CVDs such as CHD and stroke, probably for reasons of public health relevance but also for reasons of requirements of larger sample size to study less common CVDs. Another reason may relate to obstacles related to study design; as an example, AF does not always require hospitalization and the use of data from national registers may therefore be suboptimal.

The authors identify several research needs as discussed in each chapter and as summarized briefly above. Increased knowledge will allow for the identification of CVD prevention opportunities of relevance for public health. Such new knowledge on environmental influences on CVD is of importance for reliable health risk assessments, for balancing of benefits and risks, e.g. of the consumption of certain foods, for the implementation of appropriate guidelines in the international toxicological testing programs for chemicals, and also for other international work to cope with individual environmental factors or their combinations. Further, increased knowledge about biological mechanisms behind inflammation, atherosclerosis progression and thrombotic events may support conclusions about causality behind environment-disease associations and may open up for new research paths and novel ideas for improved cardiovascular prevention.

Among environmental factors that are only briefly addressed in this report are stress related factors. Work stress, as an example, is likely to remain a significant facet of the 21<sup>st</sup> century lifestyle and further research is required to determine its role in CVD pathology and how detrimental effects can be prevented. Shift work should also be included in such research efforts. Considering the strong social gradient in cardiovascular health, and that social determinants are becoming increasingly important, future research should increase knowledge about factors that may contribute to, or counteract, a distressful physical and psychosocial environment, at workplaces as well as in the accommodations and living areas. Exposure factors through the life course should be addressed, including intrauterine exposures. A future IMM report will review the current knowledge concerning intrauterine and early life exposures.

Considering the heterogeneity of CVD aetiology, it seems important for future research to separately address specific CVD diagnoses, rather than composite endpoints, when studying the influence from environmental factors. Studying subgroups of the population is also important because some groups may be more susceptible than others to certain exposures. Disease mechanisms and thus also effects of different environmental exposures may for example vary between men and women and between groups of different genetic susceptibility or cardiovascular metabolic risk profile. Future epidemiological research should aim at collecting large and well-defined study materials allowing stratified analyses and studies of interactions between risk factors.

## Konklusioner och framtida forskningsbehov

I föreliggande rapport har forskare från IMM, aktiva inom olika forskningsområden med koppling till kardiovaskulära sjukdomar, skapat en kunskapsöversikt baserad på såväl epidemiologiska som experimentella mekanistiska studier beträffande betydelsen av miljörelaterade riskfaktorer för utveckling av kardiovaskulär sjukdom. Utöver de traditionella kardiovaskulära riskfaktorerna (vilka tas upp i Kapitel 1) tycks flera andra riskfaktorer i miljön, inklusive arbetsmiljön, vara betydelsefulla och dessutom möjliga att kontrollera. För vissa faktorer, såsom exponering för luftföroreningar, finns ett starkt vetenskapligt underlag för att de observerade kopplingarna till kardiovaskulär sjukdom är kausala, medan det för andra faktorer är mer oklart huruvida de faktiskt bidrar till de orsaksmekanismer som ger upphov till kardiovaskulär sjukdom. En gemensam nämnare för flertalet av de miljöfaktorer som kopplas till ökad risk för kardiovaskulär sjukdom är en sannolik inverkan på inflammatoriska processer och ateroskleros. Det vetenskapliga stödet för sådana inflammatoriska effekter ökar stadigt för ett flertal faktorer, inkluderande vissa delkomponenter i luftföroreningar, buller och vissa metaller samt arsenik.

Matvanor har utan tvekan stor betydelse för risken att utveckla kardiovaskulär sjukdom. Kortfattat kan konkluderas att matvanor som minskar den kardiovaskulära risken kännetecknas av ett högt intag av frukt, grönsaker och fullkornsprodukter samt ett begränsat intag av socker, salt och processat kött. Kosttillskott tycks inte minska den kardiovaskulära sjukdomsrisk. Lejonparten av de nutritionsepideiologiska studier som utförts är observationella vilket kan innebära begränsade möjligheter att dra starka slutsatser såsom diskuteras i Kapitel 3. Fler interventionsstudier behövs för att bekräfta resultaten från observationella studier. Fortsatt forskning kring biologiska mekanismer som kan ligga bakom observerade samband är också motiverad. Framtida forskning bör också utreda vilken roll mikrobiomet har för kardiovaskulär sjukdomsrisk.

Exponering av långlivade organiska föroreningar (POPs), främst via föda, har associerats till ökad kardiovaskulär risk, exempelvis genom förmedling av blodtryckshöjande och blodfettshöjande effekter. Det vetenskapliga underlaget för kausala samband är dock svagt. Med tanke på att POPs finns spridda i den allmänna miljön och bioackumuleras i levande organismer finns behov av att öka kunskapen kring dessas möjliga effekter på aterosklerosutveckling och kardiovaskulär risk. Möjliga effekter från samtidig exponering för ett antal olika POPs bör också belysas.

Luftföroreningar är ett samlingsbegrepp för gaser och partiklar i luft med negativ inverkan på hälsa och miljö. Det vetenskapliga stödet för negativa effekter på kardiovaskulär hälsa är som störst för inandning av fina partiklar. Både exponering under korta och långa tidsperioder utgör viktiga faror. Luftföroreningar har i upprepade studier kopplats till ökad risk för förmaksflimmer, men det krävs mer forskning för att kunna säkerställa detta samband och utreda vilka orsaksmekanismer som kan ligga bakom.

Forskning om grönområden i städer pekar mot att sådana har välgörande effekter på den kardiovaskulära hälsan. Det är dock en utmaning för studier inom detta område att ta hänsyn till socio-demografiska faktorer samt nivåer av luftföroreningar och buller vilka kan utgöra alternativa förklaringsmodeller till att kardiovaskulär sjuklighet varierar med bostadsområdets närhet till grönområden. Trots att det vetenskapliga underlaget för hälsoeffekter av

grönområden i städer betraktas som relativt svagt förefaller det relevant för stadsplanerare att ha i åtanke det möjliga skydd som grönområden kan utgöra för befolkningens kardiovaskulära hälsa.

Det finns ett starkt vetenskapligt stöd för att höga temperaturer i omgivningen ökar risk för död i hjärt-kärlsjukdomar. Det föreligger dock regionala skillnader avseende förutsättningar att anpassa sig till värmen. Kapaciteten att klara av värmeböljor kan också skilja sig mellan olika befolkningar. Mer forskning krävs kring effekter av anpassningsåtgärder. Utöver mortalitet bör också kardiovaskulär sjuklighet beaktas.

De tre yrkesrelaterade exponeringarna som berörs i föreliggande rapport – inandningsbar kristallin kvarts, dieselavgaser och svetsrök – har alla associerats med negativa effekter på det kardiovaskulära systemet. Fler studier behövs för att bekräfta dessa fynd och för att studera dos-respons-samband. Studierna av inandningsbar kristallin kvarts är samstämmiga avseende koppling till ökad risk för hjärtinfarkt, även vid låga exponeringsdoser. Därför bör denna exponering, som till exempel finns i damm från berg vid gruvarbete eller från betong vid byggarbete, minimeras på arbetsplatser. Att vidta försiktighet avseende exponering för dieselavgaser och svetsrök är också viktigt eftersom båda dessa exponeringar kopplats till negativa effekter på det kardiovaskulära systemet, i såväl epidemiologiska som humanexperimentella studier.

Långtidsexponering för trafikbuller är associerat med ökad risk för kranskärlssjukdom. Buller på arbetsplatsen är kopplat till akut höjning av blodtryck, men riskerna för kroniskt förhöjt blodtryck och kardiovaskulär sjukdom är inte vetenskapligt belagda i samma utsträckning. Fler studier krävs för att utreda kausalitet och dos-respons-samband. Rimliga biologiska orsaksmechanismer bakom dessa associationer är de som beskrivs i modeller för hur stress påverkar det sympatiska nervsystemet och hormonella regleringar. Buller från transporter förekommer ofta samtidigt som föroreningar i luften och det är en utmaning för forskningen att särskilja effekter från dessa olika exponeringar.

För flertalet av de exponeringar som diskuteras i föreliggande rapport är kunskapsläget starkare för vissa kardiovaskulära diagnoser än andra. Detta har sin förklaring i att det gjorts mer forskning på de mest vanligt förekommande diagnoserna såsom hjärtinfarkt och stroke, antagligen av folkhälsoskäl och skäl relaterade till studiers behov av statistisk styrka. Ett annat skäl kan vara svårigheter för forskare att i sina studier identifiera sjukdomsfall med diagnoser som inte alltid kräver sjukhusinläggning, exempelvis förmaksflimmer. Utnyttjande av data från nationella register kan då vara suboptimalt.

Författarna av denna rapport har identifierat behov av mer forskning inom ett antal områden vilka diskuteras i varje kapitel och kortfattat summerats ovan. Ökningen av kunskap kommer att skapa nya möjligheter för kardiovaskulär prevention med stor relevans för folkhälsan. Med ökad kunskap om miljöfaktorer i relation till kardiovaskulär sjukdom kan bedömningar av hälsorisker göras säkrare, nytta vägas bättre mot risker (exempelvis avseende vissa livsmedel), och lämpliga riktlinjer utformas i de internationella toxikologiska testprogrammen för kemikalier samt i annat internationellt arbete för att hantera individuella miljöfaktorer eller deras kombinationer. Vidare ger ökad kunskap om biologiska mekanismer bakom inflammation, progression av ateroskleros och trombotiska händelser stöd för slutsatser om orsakssamband bakom observerade samband mellan miljöfaktorer och kardiovaskulär



sjukdomsrisk och kan öppna upp för nya forskningsvägar samt nya idéer för förbättrad kardiovaskulär prevention.

Bland de miljöfaktorer som endast kortfattat berörts i föreliggande rapport är stress-relaterade faktorer. Stress i arbetsmiljön, exempelvis, förblir sannolikt en betydande aspekt för tjugohundratalets livsstil och mer forskning krävs för att fastställa dess roll för utveckling av kardiovaskulär sjukdom och hur skadliga effekter kan motverkas. Forskning kring skiftarbete bör också ingå i dessa ansträngningar. Med tanke på den starka sociala gradienten inom kardiovaskulär hälsa och att sociala determinanter blir allt viktigare, bör framtida forskning öka kunskapen om faktorer som kan bidra till, eller motverka, en riskfylld fysisk och psykosocial miljö, såväl på arbetsplatser som i bostaden och bostadsområdet. Exponeringar genom hela livet bör beaktas, inklusive intrauterina exponeringar. En kommande IMM-rapport kommer att granska kunskapsläget avseende intrauterin och tidig exponering i livet.

Med tanke på att kardiovaskulär sjukdom är etiologiskt heterogen förefaller det viktigt att framtida forskning separat adresserar specifika kardiovaskulära diagnoser, snarare än sammansatta diagnosgrupper, vid studier av påverkan från miljöfaktorer. Studier av undergrupper av befolkningen är också viktiga då vissa grupper kan vara mer känsliga än andra för vissa exponeringar. Sjukdomsmekanismer och därmed även effekter av olika miljöexponeringar kan exempelvis variera mellan män och kvinnor och mellan grupper med olika genetisk känslighet eller kardiovaskulär metabolisk riskprofil. Framtida epidemiologisk forskning bör syfta till att samla stora och väldefinierade studiematerial som möjliggör stratifierade analyser och studier av interaktioner mellan riskfaktorer.

## 11. Glossary

Aortic disease	A split (dissection) or dilatation (aneurysm) of the aorta, which may rupture and have a fatal outcome.
Atrial fibrillation (AF)	A quivering or irregular heartbeat (arrhythmia) that can lead to blood clots, stroke, heart failure and other heart-related complications. Also known as Afib.
Cardiomyopathy	A myocardial disorder in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular disease, and congenital heart disease sufficient to explain the observed myocardial abnormality.
Cardiovascular disease (CVD)	Diseases of the circulatory system. A group of disorders of the heart and blood vessels that include CHD, cerebrovascular disease, PAD, rheumatic heart disease (damage to the heart muscle and heart valves from rheumatic fever, caused by streptococcal bacteria), congenital heart disease (malformations of heart structure existing at birth), deep vein thrombosis and pulmonary embolism (blood clots in the leg veins, which can dislodge and move to the heart and lungs). Heart attacks and strokes are usually acute events and are mainly caused by a blockage that prevents blood from flowing to the heart or brain. The most common reason is a build-up of fatty deposits on the inner walls of the blood vessels.
Cerebrovascular infarction (stroke)	Disease of the blood vessels supplying the brain. Strokes can be caused by bleeding from a blood vessel in the brain or by blood clots.
Coronary heart disease (CHD)	Disease of the blood vessels supplying the heart muscle. Also termed coronary artery disease (CAD) and ischemic heart disease (IHD).
Ecologic study design	Observational study design where group level data, rather than individual level, are used.
Heart failure	Severe failure of the heart to function properly. Also known as chronic heart failure.
In vitro studies	Experiments conducted outside of a living organism. “In vitro” is Latin for “within the glass”.
In vivo studies	Experiments that use a whole, living organism. “In vivo” is Latin for “within the living”.

Longitudinal study design	Prospective research design that involves repeated observations of the same variables over time.
Mendelian randomization study	Study design that uses genetic variation related to risk factors of interest in efforts to re-assess observational estimates.
Metabolic syndrome	A cluster of conditions that occur together, increasing the risk of heart disease, stroke and type 2 diabetes. These conditions include increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels.
Myocardial infarction (MI)	A sudden decreased or stopped blood flow to a part of the heart, causing necrosis of the heart tissue. Also known as acute MI (AMI) and heart attack. The interruption of blood is usually caused by narrowing of the coronary arteries leading to a blood clot.
Peripheral artery disease (PAD)	Disease of blood vessels supplying the arms and legs.
Reverse causality	Direction of cause-and-effect contrary to a common presumption.
Stroke, haemorrhagic	Either a brain aneurysm burst or a weakened blood vessel leak causing bleeding that suddenly interferes with the brain's function. There are two types of haemorrhagic stroke called intracerebral and subarachnoid.
Stroke, ischemic	A blood vessel carrying blood to the brain is blocked by a blood clot. This causes blood not to reach the brain.

## 12. Abbreviations

ACE, angiotensin converting enzyme  
AF, Atrial fibrillation  
AHA, American Heart Association  
AhR, aryl hydrocarbon receptor  
AMI, acute myocardial infarction  
Anti-MDA, antibodies against malondialdehyde  
Anti-PC, antibodies against phosphorylcholine  
BFR, brominated flame-retardants  
BMI, body mass index  
CAD, coronary artery disease  
CAR, constitutive androstane receptor  
CI, confidence interval  
CIMT, intima-media thickness of the common carotid artery  
CVD, Cardiovascular disease  
CVP, central venous pressure  
CHD, coronary heart disease  
CO, carbon monoxide  
COPD, chronic obstructive pulmonary disease  
COSM, Cohort of Swedish Men  
COX-2, cyclooxygenase  
CRP, C-reactive protein  
DASH, Dietary Approaches to Stop Hypertension  
DC, dendritic cells  
DDE, p,p'-dichlorodiphenyldichloroethylene  
DDT, dichlorodiphenyltrichloroethane  
DME, diesel motor exhaust  
EC, elemental carbon  
ECG, electrocardiogram

EFSA, European Food Safety Authority  
ESCAPE, European Study of Cohorts for Air Pollution Effects  
HCB, hexachlorobenzene  
HDL, high density lipoprotein  
HPA, hypothalamic pituitary adrenal  
HR, hazard ratio  
HRV, heart rate variability  
HSP, heat shock protein  
IARC, International Agency for Research on Cancer  
ICD, International Statistical Classification of Diseases and Related Health Problems  
ICD, implantable cardioverter defibrillator  
IHD, Ischemic heart disease  
IRR, incidence rate ratio  
IL, interleukin  
IMT, intima-media thickness  
JEM, job-exposure matrix  
LDL, Low density lipoprotein  
LDLR, Low density lipoprotein receptor  
MDA, malondialdehyde  
MESA, Multi-Ethnic Study of Atherosclerosis  
MI, Myocardial infarction  
MOR, mortality odds ratio  
NHANES, US National Health and Nutrition Examination Survey  
NO, nitric oxide  
NO<sub>x</sub>, nitrogen oxides  
NDVI, Normalized Difference Vegetation Index  
OxLDL, Oxidized low density lipoprotein  
OC, organic carbon  
OC, organochlorine  
OR, odds ratio

PAD, Peripheral artery disease

PAF, platelet activating factor

PBDE, polybrominated diphenyl ether

PC, phosphorylcholine

PCB, polychlorinated biphenyls

PFAS, perfluoroalkyl and polyfluoroalkyl substances

PFNA, perfluorononane acid

PFOA, perfluorooctanoic acid

PFOS, perfluorooctane sulphonate

PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors

PM<sub>x</sub>, particulate matter with diameter less than x μm

PMR, proportionate mortality ratio

PNC, particle number concentration

POP, persistent organic pollutant

RCS, respirable crystalline silica

RCT, Randomized controlled trial

PCDD, polychlorinated dibenzo-*p*-dioxins

PPARα, peroxisome proliferator-activated receptor alpha

PXR, pregnane X receptor

RR, relative risk

ROS, reactive oxygen species

SAM, Sympathetic-Adrenal-Medullary

SBU, Statens Beredning för Medicinsk och Social Utvärdering (Swedish Agency for Health Technology and Assessment of Social Services)

SD, standard deviation

SHEEP, Stockholm Heart Epidemiology Program

SMC, Swedish Mammography Cohort

SMR, standardized mortality ratio

SO<sub>2</sub>, sulfur dioxide

T2DM, type 2 diabetes

TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin

TNF, tumor necrosis factor

TWI, tolerable weekly intake

VIP, Västerbotten Intervention Programme

WHO, World Health Organization

ys, years

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