

Chapter 2

Exposure to Environmental Hazards and Effects on Chronic Disease

Miranda Loh

Abstract There are numerous hazards that people are exposed to in everyday life: at home, at work, and in other locations (microenvironments). Between exposure and health effect there are a large number of modifying risk factors, as embodied in the concept of the exposome. Exposures to other hazards, genetics, and society all play a role in whether and how an exposure results in an adverse effect. The timing of exposure is also an important factor. In utero and early life exposures may be of particular importance for initiating some types of diseases that manifest later in life.

Chronic diseases such as cardiovascular and respiratory disease are important contributors to the global burden of disease. These diseases are a result of the interplay of several risk factors, which include environmental exposures. The exposomic approach is therefore particularly applicable to the study of environmental causes of chronic disease. Rather than take a pollutant-by-pollutant focus, this chapter will examine two common chronic diseases which research has shown to have multiple contributing environmental risk factors. The proposed diseases are cardiovascular disease and non-malignant respiratory disease (particularly asthma). The chapter will cover both acute and chronic effects, including a discussion of the evidence for some hazards where exposures in childhood or before birth can potentiate future disease.

Keywords Exposome • Exposure • Cardiovascular disease • Asthma

2.1 Introduction

There are numerous hazards that people are exposed to in everyday life: at home, at work, and in other locations (microenvironments). Health impacts of environmental hazards are a product of many different factors. These factors can be co-exposures, epigenetics, genetics, psychosocial stress, the physical environment, cultural factors,

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etc. Whereas in the past, research into health impacts of environmental exposures tended to focus on eliciting the effect of a single hazard, while controlling for potential confounding factors, the research paradigm is moving towards a multi-factorial approach. The idea of “-omics” embodies this approach, where “-ome” refers to the totality of something, the genome, the transcriptome, the microbiome, etc. Methods of analysis—chemical, biological, and statistical—are now more focused on evaluating multiple risks as a whole, examining risk profiles, rather than single predictors.

Exposure science is now faced with the “exposome”, or all exposures that a person experiences from conception to death (Wild 2012). It is thought that only a small percentage of disease is explained by genetic factors (Thomas 2010). Gene-environment interactions likely play an important, but not well understood role in disease development. These include a wide range of factors, which can be grouped as general external (e.g. urban environment, psychosocial stress), specific external (e.g. air pollutants, radiation), and internal (e.g. genetics, inflammation) as reflected in Fig. 2.1. The interaction of these spheres results in disease manifestation. The challenge for the future will be developing frameworks and methodologies for assessing the exposome. Although it may be impossible to assess all aspects of the exposome, at least in the near future, it is important to begin taking this approach for understanding and preventing disease.

This chapter will examine two common chronic diseases which research has shown to have multiple contributing environmental risk factors. The proposed diseases are cardiovascular disease and asthma. Chronic diseases such as these

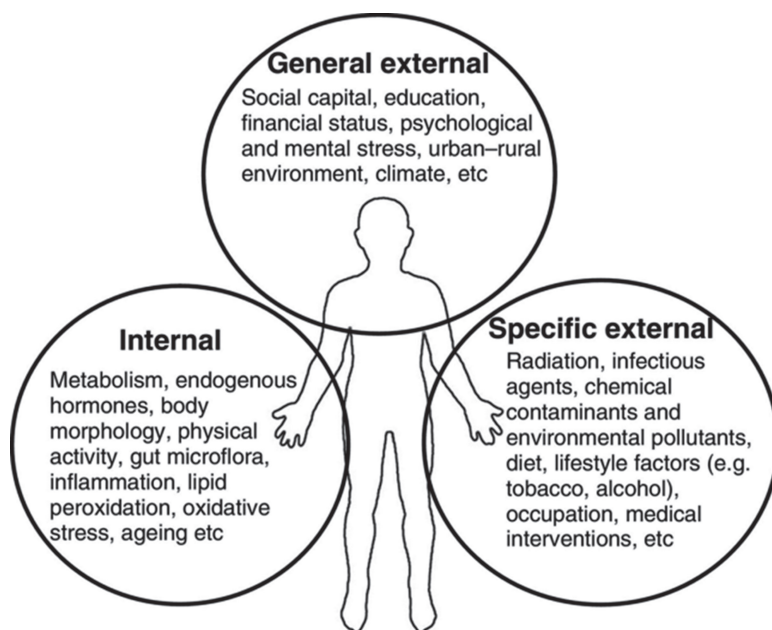


Fig. 2.1 The exposome (Wild 2012) by permission of Oxford University Press

are important contributors to the global burden of disease, and are a result of the interplay of several risk factors, which include environmental exposures. The exposomic approach is therefore particularly applicable to the study of environmental causes of chronic disease. Although the pathways through which the environment influences the development and manifestation of these diseases differ, inflammation is a key common mechanism of action. There are a number of hazards and risk factors that affect both heart and lung disease, including exposure to air pollution, arsenic, cigarette smoke (and smoking), diet, obesity, and stress. Exposures *in utero* and in early life are also thought to be an important influence on the later development of disease. This chapter will not discuss exposures to parents pre-conception, but includes a brief discussion of exposures via the mother *in utero*. In the fetal origins of disease theory, exposures *in utero* may make a person more susceptible to disease later on in life. Exposures and lifestyle patterns after birth and into adulthood also affect the propensity of the person to develop disease as an adult.

The chapter will cover both acute and chronic effects, including a discussion of the evidence for some hazards where exposures in childhood or before birth can potentiate future disease. The focus will be primarily on the “specific external” exposome, with some discussion of how “general external” factors may contribute to disease effects. Internal aspects will not be examined. The factors described here are meant to cover many of the non-occupational risk factors for Cardiovascular disease (CVD) and asthma, but are not a complete list.

2.2 Cardiovascular Disease and Asthma

2.2.1 Cardiovascular Disease

Cardiovascular diseases (CVD) are the leading cause of death globally, and ischemic heart disease is estimated to be responsible for about half of all CVD deaths. Genetics and lifestyle play a key role in development of disease, but environmental risk factors are also an important contributor. Risk prediction based on the Framingham Heart Study for heart disease outcomes such as myocardial infarction, coronary heart disease, and death, include age, gender, total serum cholesterol, high density lipoproteins (HDL), blood pressure, diabetes, and smoking (D’Agostino et al. 2001). Ethnic and racial groups exhibit differences in CVD risk. Tobacco, low HDL and high low density lipoproteins (LDL), and elevated glucose are accepted as causal risk factors for CVD, while external risk factors that predispose individuals to CVD include physical inactivity, socioeconomics, stress, and diet (Yusuf et al. 2001). Exposure to several pollutants has also been found to increase risk of developing cardiovascular disease, and contribute to inducing acute cardiovascular events. Inflammation is a key mechanism by which many non-genetic risk factors, including environmental ones, are thought to influence development of CVD.

2.2.2 Asthma

Asthma is a complex disease of the airways, with several phenotypes (observable characteristics) and endotypes (disease entity defined by a specific biological mechanism) (Lötvall et al. 2011). Allergic phenotypes tend to occur in youth, and are more likely in males, although they can still manifest in adulthood. The onset of asthma in childhood is greater in males than females, whereas in adulthood the pattern is switched. Non-allergic asthma tends to occur more often in adulthood. A number of environmental agents have been found to play a role in impacting the development of the lung, and hence susceptibility to lung disease in childhood or adulthood (Miller and Marty 2010). Asthma can be characterized by chronic inflammation, which leads to airway hyper-responsiveness and remodeling (Bousquet et al. 2000), although there have been observations that not all asthma patients have a strong inflammatory component (Lötvall et al. 2011).

2.2.3 Common Exposures and Risk Factors for Cardiovascular Disease and Asthma

Major “specific external” exposome factors that play a role in development and symptom manifestation of both CVD and asthma include exposures to air pollution, cigarette smoke, arsenic, and diet (Fig. 2.2). Psychosocial stress and socioeconomic status are also “general external” exposome factors for both sets of diseases. Specific occupational exposures can also play an important role for development and exacerbation of CVD and asthma, although these are not described in detail in this chapter. Other exposures related to CVD include noise and metals, while those related to asthma include cleaning product chemicals, phthalates, and dampness and mould.

2.2.3.1 Air Pollution

Much of the evidence around air pollution risks relates to combustion-source pollutants. Exposure to these pollutants can take place outdoors, in transit, at work, and indoors. Outdoor sources include power plants, industry, residential wood burning, vehicles, and ships. Indoor sources include smoking, cooking, candle and incense burning, and fireplaces. Outdoor sources are the most easily controlled by regulatory authorities and policies, but people spend relatively little time outdoors (~ less than 10 % of time, on average) (Klepeis et al. 2001; Schweizer et al. 2007).

Air pollution is a complex mixture of gases and particulate matter, which is determined by sources and atmospheric or microenvironmental climate and conditions. The mixture of pollutants a person breathes in depends on the location of the person

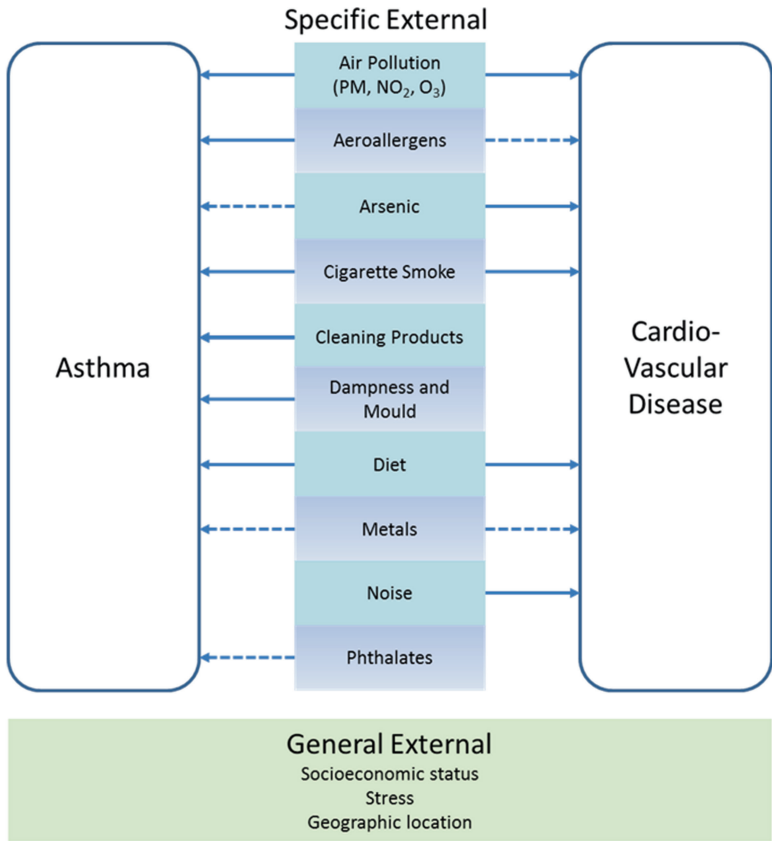


Fig. 2.2 Aspects of the external exposome that influence asthma and cardiovascular disease. The *solid arrows* indicate relatively strong evidence for either symptoms or induction of disease and the *dashed arrows* indicate suggestive but not conclusive evidence

and the sources that contribute to the pollution in that location. Outdoor sources include power plants, industry, residential wood burning, vehicles, and ships along with natural sources such as desert dust (in some regions) and wildfires.

Of outdoor sources, traffic pollution is of particular concern because this source tends to be closer to the population as a whole, especially in urban areas. People therefore have a greater risk of exposure to traffic pollution. Epidemiology studies have also found associations between exposure to traffic and cardiovascular disease and asthma. Traffic pollution includes particulate matter (PM), nitrogen dioxide, carbon monoxide, aldehydes, volatile organic compounds (VOCs), and semi-volatile compounds (SVOCs), such as polycyclic aromatic hydrocarbons (PAHs). One difficulty with assessing the health impacts for pollutants from a common source, such as traffic, is that the concentrations tend to be correlated, thus making it difficult to separate the effects of one pollutant from another. Controlled exposures or laboratory studies provide some possibility of distinguishing the individual effects of pollutants.

Particulate matter has been strongly related to cardiovascular disease in epidemiology, toxicology, and controlled exposure studies (Brook et al. 2010; Miller et al. 2012). Evidence for the effects of ozone and nitrogen dioxide on cardiovascular disease is not as clear as for particulate matter (Review of evidence on health aspects of air pollution—REVIHAAP project 2013). In chamber studies, exposures to concentrated ambient particles or dilute diesel exhaust led to acute vasoconstriction in volunteers, but exposures to NO₂ and filtered air showed no effects on vascular dysfunction (Langrish et al. 2010). Exposure to NO₂ may increase the effects of particulate matter, although this has not been demonstrated in all areas (Brook et al. 2004).

Nitrogen dioxide is often used as a marker of traffic exhaust, and there is some evidence in the time series literature for respiratory related mortality (Review of evidence on health aspects of air pollution—REVIHAAP project 2013). Nitrogen dioxide levels in homes with gas appliances has been found to range from 180 to 2500 µg/m³, which are many times higher than typical outdoor levels (Heinrich 2011). In controlled exposure studies NO₂ leads to sustained increases in neutrophil response and decreases in lung function in healthy subjects, but only when exposure is >1 ppm, which is about two orders of magnitude greater than typical outdoor exposures (Parnia et al. 2002). Evidence is less clear for lower concentrations, which are what people are exposed to in daily life. Nitrogen dioxide may play a role in exacerbating asthma, and has been associated with incident wheeze, but it is uncertain whether or how nitrogen dioxide influences the development of asthma. A modest association between NO₂ and incidence of asthma (OR 1.09, 0.96–1.23 per 10 µg/m³ increase) was found in a meta-analysis of five birth cohorts for longitudinal exposure and childhood asthma, but with substantial variability between studies (Bowatte et al. 2015). Co-exposures of more than one air pollutant have been found to increase the airway response of the allergic asthmatic response to triggers (Parnia et al. 2002).

Ozone exposure is also associated with asthma symptoms, exacerbations, and decreased lung function in adults. It has been shown to induce inflammation in the lung, and animal studies indicate that ozone exposure leads to airway remodeling (Review of evidence on health aspects of air pollution—REVIHAAP project 2013). Experimental exposure of humans to ozone causes irritation and cough, with decrements in FVC and FEV₁, but at high levels (0.4 ppm) (Koren et al. 1989). Inflammatory biomarkers were also shown to increase, along with indicators of increased vascular permeability. Such effects may allow allergens to penetrate deeper into airway mucosa, increasing or altering the immune response (Parnia et al. 2002).

Particulate matter itself is a mixture of particles of different sizes and composition. PM is a trigger for short-term cardiovascular events, and for biological responses that can raise long-term CV risk (Brook et al. 2010). Several characteristics of PM are thought to play a role in its toxicity: size, surface area, and composition. These characteristics are linked to the sources that emit PM and the physio-chemical transformations that the particles undergo in the atmosphere. Although particles of various sources have been linked with CVD, combustion-produced particles are of particular interest, due to the small size of these particles, and the potential for

numerous toxins to be sorbed onto these particles. One mechanistic explanation for the effect of PM on CVD is through the inflammatory response. Inhalation of particles leads to inflammation in the airways, with fine and ultrafine particles reaching the alveolar region. Particles less than a nanometer in size may cross the alveolar membrane and enter systemic circulation.

In occupational settings, particles are classified into three sizes. Inhalable particles enter the nose and mouth through breathing, and are 100 μm in diameter or less. These may include dusts and other mechanically generated particles. Thoracic particles ($\leq 20 \mu\text{m}$ diameter) penetrate further into the bronchi, and respirable particles ($\leq 4 \mu\text{m}$ diameter) yet further into the alveoli. Non-occupational regulations distinguish between PM_{10} and $\text{PM}_{2.5}$, which are particles with an aerodynamic diameter $\leq 10 \mu\text{m}$ and $\leq 2.5 \mu\text{m}$, respectively. $\text{PM}_{2.5}$ is also known as fine particulate matter, while particles between 2.5 and 10 μm are termed coarse particles. Fine particles are generally emitted from combustion sources, such as fires, power plants, and vehicles, and from secondary formation from gases or liquid droplets. Coarse particles in the environment can include dust, such as re-suspended road dust and desert dust. Biological aerosols such as pollen, mould, allergens from insects and pets, bacteria, and viruses can be found throughout the range of particle sizes. Freshly emitted particles from traffic are in the ultrafine range ($< 100 \text{ nm}$). Ultrafine particle (UFP) concentrations tend to drop off relatively quickly from the road, with levels reaching background around 300 m, with a 50% reduction by about 150 m (HEI Review Panel on Ultrafine Particles 2013).

In addition to size, particulate matter can differ widely in composition from source to source. Healthy volunteers exposed to diesel exhaust particulate in controlled exposure studies have been found to induce responses such as inflammation, endothelial dysfunction, and thrombosis (Lucking et al. 2008; Lundbäck et al. 2009; Törnqvist et al. 2007). Exposure to particles of different composition in controlled exposure studies (i.e. concentrated ambient particulates, CAPS, and diesel exhaust) showed differing effects on heart rate variability, with reductions in variability seen with CAPS but not with diesel (Miller et al. 2012). Individual constituents of particles such as certain metals may affect risk of CVD development.

Although combustion source particles are thought to be most dangerous for health, time series studies have also found that desert dust can impact mortality and hospital admissions (Middleton et al. 2008; Perez et al. 2008). Particles from indoor sources may also be from combustion sources, dust, biological material, or secondary organic aerosols, generated from reactions between volatile organic compounds and ozone. Health effects of indoor source particles are less well studied, and it is assumed that combustion source indoor particles would have the same effect as ambient particles. However, the inflammatory response to particles in the respiratory tract may be a key mechanism, in the development and exacerbation of CVD, thus implying that all particles may be of concern.

Air pollutants have been clearly shown to increase the risk of asthma exacerbations and symptoms, and may also increase risk of developing asthma, especially in children (Gowers et al. 2012). Traffic exhaust exposure is associated with higher risk of asthma symptom development. Ozone, nitrogen dioxide, and particulate matter, all

also related to traffic, have been associated with asthma exacerbation. A multi-cohort study of more than 23,000 adults followed over 10 years was suggestive of an effect from NO_2 and PM_{10} on asthma development, but results were not conclusive (Jacquemin et al. 2015). A review by the British Committee on the Medical Effects of Air Pollutants (COMEAP) determined that evidence for individual pollutants in asthma induction is still inconclusive, but studies indicate that living close to major roads (<150 m) is linked to wheeze and asthma, with increasing effects with proximity (Gowers et al. 2012). In addition, truck traffic has been identified as a risk for asthma, which may be considered a proxy for increased exposure to diesel exhaust.

Particulate matter elicits an inflammatory response and contains aeroallergens, metals, PAH, and other substances that may trigger both allergic and non-allergic airway responses. A meta-analysis of four birth cohort studies found an increased incidence of childhood asthma (OR 1.14, 1.00–1.30 per $2 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$) but also with substantial heterogeneity between studies (Bowatte et al. 2015). Diesel exhaust particulate (DEP) has been identified as a possible carrier of allergens on surface, therefore increasing exposure during pollution episodes, or near roads with diesel traffic (Parnia et al. 2002). DEP have been shown to enhance IgE production and activation of basophils, particularly due to the polycyclic aromatic hydrocarbons (PAH) on the particle surface rather than carbon core (Lubitz et al. 2010; Parnia et al. 2002; Takahashi et al. 2010), but do not induce IgE production. Also, DEP causes inflammation of the airways, which makes them more susceptible to allergen challenge. Damage to epithelium and cilia reduces the effectiveness of the biological barrier against allergens (Parnia et al. 2002). In general, PM has been associated with asthma symptoms, but evidence for development of asthma is limited, although *in utero* exposure to $\text{PM}_{2.5}$ has been associated with early childhood asthma (Hsu et al. 2015).

An important source of exposure for many air pollutants is cigarette smoke. Smoking is a known risk factor for cardiovascular and respiratory diseases, including asthma. In addition, non-smokers chronically exposed to cigarette smoke are similarly at risk (Barnoya and Glantz 2005; Öberg et al. 2011; Pope et al. 2009). Exposure to second hand smoke (SHS) is of particular concern indoors, where due to a smaller volume for dilution and, in some homes, lower ventilation rates, the accumulation of particles and other pollutants from cigarette smoking can lead to quite high levels of pollutants (Callinan et al. 2010; Loh et al. 2006; Nazaroff and Singer 2004; Semple et al. 2012; Waring and Siegel 2007). For example, the concentration of $\text{PM}_{2.5}$ and benzene in Irish pubs decreased approximately 80 % from pre-ban levels after the Irish ban on workplace smoking (Goodman et al. 2007). These bans have also been found to decrease hospital admissions for cardiovascular and asthma outcomes (Cesaroni et al. 2008; Goodman et al. 2007; Sims et al. 2010). While smoking bans in workplaces and public buildings have become more prevalent in many countries, smoking may still occur inside homes and private vehicles.

In vivo studies of exposure to diesel exhaust and cigarette smoke show that *in utero* and in early life exposures can induce physiological changes that increase the risk of cardiovascular related risk factors (e.g. blood pressure, weight gain) in adult mice (Weldy et al. 2014). Some epidemiological studies have found that

prenatal exposure to air pollution results in birth outcomes indicating reductions in fetal growth (e.g. small for gestational age, low birthweight, low intra-uterine growth rate), which may be associated with CVD later in life (Ballester et al. 2010; Šrám et al. 2005).

2.2.3.2 Noise

Noise exposure may contribute to the development of CVD due to stress or activation of the sympathetic nervous system, and has been associated with increased blood pressure, changes in heart rate, and release of stress hormones (Babisch 2011; Basner et al. 2014). Overall, road traffic and aircraft noise seems to have an independent effect on CVD and hypertension from air pollution, although effects and significance across epidemiology studies are mixed (Davies and Kamp 2012). Nocturnal noise is considered more important than daytime noise, especially with respect to sleep disturbance.

The HYENA study of noise near Heathrow Airport in London found significant increases in blood pressure with night noise, but not with daytime noise. Cohort studies, which investigate long-term exposure to noise, have found increased hypertension with road traffic noise, with a meta-analysis showing an odds ratio of 1.08 (1.04–1.13) per 10 dB increase in L_{DN} (day-night equivalent level, over 24 h, with an additional penalty for night-time noise), where noise levels were in the range of 50–75 dB (Münzel et al. 2014). Sleep restriction or fragmentation is another factor that affects the development of various CVD risk factors, and has been associated with inadequate pancreatic insulin secretion, decreased insulin sensitivity, changes in appetite regulating hormones, increased sympathetic tone, and venous endothelial dysfunction (Münzel et al. 2014). Habitual sleep of less than 6 h per night has been related to obesity, diabetes, hypertension, CVD-related and all-cause mortality (Münzel et al. 2014). Vulnerable groups such as the elderly, shift workers, and those with illness may be more susceptible to noise related sleep disturbance (WHO 2009). These groups are also more vulnerable to other environmental risks for CVD, particularly air pollution.

In non-occupational settings, noise exposure from transportation-related sources has been most studied, especially with road and aircraft noise. Road noise is often correlated with air pollutants released by vehicles, and therefore these must both be considered in analyses. Noise exposure has two components: a measure of loudness (sound pressure level) and frequency. Loudness is generally what is used to define noise exposure in epidemiology studies, but frequency is also an important characteristic. The frequency of a noise can affect a person's perception of the annoyance of noise, even if the noise is not loud. High frequency noises are also easier to dampen than low frequency noise, due to the much shorter wavelength of high frequency noises. Masking of one noise source with another also depends on whether the noise sources' frequency domains overlap (WHO 2009). The intervals at which a noise occurs can also affect the health impact of noise.

Noise can be monitored using sound level meters for area measurements, or dosimeters, for personal measurements. In many epidemiology studies, however, noise exposure is modeled at the outer façade of a building, based on inputs such as traffic flow and road type. Noise exposure is generally reported as $L_{Aeq,T}$, which refers to A-weighted sound pressure level in decibels averaged over an amount of time, T . The A-weighting refers to a means of correcting sound pressure levels for the frequencies to which the human ear is most sensitive. Day (L_{day}) and night (L_{night}) noise where sound pressure levels are averaged over specified daytime and nighttime hours may be used as metrics of environmental noise exposure. Additionally, the L_{den} may be used, where noise levels in the daytime, evening, and night are differentially weighted, with the greatest penalty for night-time noise. While the sound pressure levels only refer to loudness, it is assumed that they are specific to noise of a particular source and frequency domain.

Transport-related noise levels are relatively lower than levels at which occupational noise is regulated. Low noise exposure assignment is <50 dBA, while high exposures are >60, however noise below 40 dBA may disturb sleep (Münzel et al. 2014; WHO 2009). The World Health Organisation (WHO) recommends that noise be assessed for relevant locations in the home at different times of the day, such as the bedroom for nighttime noise. However, this resolution of data is not generally available. Sound dampening of buildings can account for from 24 to over 45 dB of reduction of outdoor source noise. Noise from other sources in the home, or noise at non-home locations that people spend time in are not included when examining the health impacts of noise.

2.2.3.3 Metals

Certain elements have been found to influence the development of CVD and asthma, generally at high levels of exposure. Much of the evidence, especially for asthma, is seen in occupational exposures, for example in smelter workers, welders, and similar jobs working with high metal exposures. Cigarettes are also a significant source for smokers and those with frequent exposure to environmental tobacco smoke. There is support for a link between lead exposures, especially at high levels as seen in occupational settings, and hypertension, although the evidence for the effect at low environmental exposures is not clear (Bhatnagar 2006; Hu et al. 1996; Navas-Acien et al. 2007). The mechanism of action is still unknown, but may involve changes in renal function and oxidative stress (Vaziri 2008). There has been some suggestion that cadmium and mercury exposure may also influence the development of CVD, but these effects are not yet well supported by the literature. Exposure to metals tends to be via ingestion (dietary and non-dietary) or inhalation, with varying absorption efficiencies depending on the route of exposure and medium of exposure (e.g. water, food, dust, or soil) (Solenkova et al. 2014). For most people, cadmium and mercury exposure would come from food. Leafy vegetables, potatoes, grains, some nuts and legumes, and organ meats have high levels of cadmium (EFSA (European Food Safety Authority) 2012; Solenkova et al. 2014). Mercury

intake can be particularly high for those who eat certain types of fish, or marine mammal meat. Other sources include certain cosmetics, dental amalgams, and medicines (Solenkova et al. 2014).

Lead exposures have declined greatly in many countries, with the removal of lead from gasoline, paint, and common products. Occupational groups, those living in homes with lead paint, or those living near industries such as smelters are vulnerable to high exposures. In the United States, the Centers for Disease Control (CDC) reduced the guideline for blood lead from 10 to 5 $\mu\text{g}/\text{dL}$. Ingestion of lead is of most concern for children, although in areas where the particle load of lead is high, inhalation may be an additional exposure route. Exposures can exceed the guidelines even for non-occupational groups for people who live near lead-emitting industries (Gulson et al. 1994; Wilson et al. 1986). In some countries, lead may still be present in pottery glazes or glassware used for food, and this may be an additional pathway of exposure. Occupational exposures most likely occur from inhalation of lead fumes or lead dust, and from ingestion of lead dust. Occupations at greater risk for lead exposure include those that manufacture or use ammunition, recycling of electronics, metal, or batteries, welders, and workers in lead mining, refining, or smelting. Occupational limits are 50 $\mu\text{g}/\text{m}^3$ in the US and UK.

2.2.3.4 Arsenic

Arsenic exposure is near ubiquitous, as it is found in many foods, both naturally and as a contaminant. Arsenic is a metalloid that people are commonly exposed to either as inorganic arsenic, As(III) or As(V), which are thought to be of most concern, and also as organic species. In addition to chronic lifetime exposures, *in utero* exposure to arsenic has been associated with increased risk of CVD. Inhalation exposure is a relatively small contributor to total arsenic exposure, except in occupational settings. Arsenic may be found bound to particles in the air and in soil, and can be present in high concentrations in certain regions due to a region's geological characteristics, or due to contamination, such as in areas near copper smelters or mines. Arsenic in soil or indoor dust may be inadvertently ingested, a pathway of exposure that infants and toddlers are particularly susceptible to. In areas with high arsenic in soil or dust, arsenic in urine in young children has been found to be correlated with soil or dust concentrations. The major pathways of exposure to arsenic, however, are ingestion of contaminated drinking water and food.

Arsenic exposure has been linked to increased risk of developing cardiovascular diseases and related risk factors of hypertension and diabetes and decreased lung function, bronchiectasis, and increased susceptibility to respiratory infections. Although arsenic is associated with reduced lung function and respiratory infection, it has not yet been found to be related to asthma. It was, interestingly, considered an anti-asthmatic in earlier times. Health effects have primarily been observed in populations with relatively high exposures via contaminated drinking water. Effects at lower levels, which many more people are exposed to, are not conclusive.

Chronic exposure to high levels of arsenic in drinking water (>100 ppb) is related to hypertension and CVD in various populations around the world. In a meta-analysis, Moon et al. found pooled relative risks comparing the highest to lowest exposure groups of 1.32 (95 % CI 1.05–1.67) for CVD, 1.89 (1.33–2.69) for coronary heart disease, 1.08 (0.98–1.19), and 2.17 (1.47–3.20) for peripheral artery disease (Moon et al. 2012). Exposure at low to moderate levels (<100 ppb) shows mixed results for an effect on CVD and related disease. The WHO recommends a limit of 10 ppb of arsenic in drinking water. Arsenic in drinking water is of most concern in areas where it is present in the mineralogy of an area and leaches into the ground water drinking supply. Well known high contamination cases have occurred in Bangladesh, China, Chile, among others. Anthropogenic activities, such as mining, can also lead to contamination of ground water if not controlled.

A study in Chile of adults who were exposed *in utero* to high levels of arsenic in drinking water (>800 ppb) were at higher risk of bronchiectasis, a chronic obstructive lung disease (Dauphine et al. 2013). Studies in mice have found that exposures *in utero* and in early life around the current and past drinking water standards (10 ppb and 50 ppb, respectively), can induce airway hyper-responsiveness and changes in gene regulation for collagen and elastin, indicating that structural changes occur early on that may lead to lung disease (Lantz et al. 2009). Although high arsenic exposures from water ingestion are only prevalent in certain parts of the world, the role of exposures through dietary ingestion on health outcomes is less well known. Vitamin and mineral deficiencies have been found to decrease methylation capacity for inorganic arsenic, which may therefore increase susceptibility to the toxic effects of arsenic. Deficiencies in protein, folate, iron, zinc, niacin, vitamin E and B₁₂ have been associated with decreases in arsenic methylation (Gamble et al. 2006; Steinmaus et al. 2005).

Dietary ingestion may also be a significant source of exposure to arsenic. In areas where there are no sources of water or soil/dust contamination, diet is the main source of exposure (Kurzius-Spencer et al. 2014). Some foods naturally have arsenic, such as seafood and some types of seaweed (Moreda-Pineiro et al. 2012; Navas-Acien et al. 2011; Sirot et al. 2009). Seafood tends to be high in arsenobetaine, an organic arsenic species that is thought to be non-toxic. Certain plant species are known to effectively uptake arsenic if it is present in the growing medium (Ramirez-Andreotta et al. 2013a). Rice is a staple crop, grown, exported, and used around the world. In recent years, high levels of arsenic have been found in rice grown in various areas, including Asia and the United States (Adomako et al. 2009; Juhasz et al. 2006; Rahman et al. 2009). Vegetables grown in home gardens in areas where the soil has high arsenic content may also uptake arsenic and can be an additional pathway for arsenic intake for residents in areas where arsenic is naturally high in the soil or where the ground may be contaminated by nearby industry or industrial waste (Ramirez-Andreotta et al. 2013a, b). The role of food-related exposure to arsenic on the development of health effects has not been extensively studied.

Occupational exposure to arsenic mainly occurs in copper or lead smelting industries, those working with arsenic-containing antifungal wood preservatives, anti-fouling paints, pigments, pesticides, glass manufacturing, or coal-fired power plants that use coal with high arsenic content. Occupational air exposure limits are 10 µg/m³ (US OSHA).

2.2.3.5 Diet and Physical Activity

Diet and physical activity are key protective factors against many types of disease. Physical inactivity and poor diet lead to obesity and diabetes, dyslipidemia, and can increase inflammation in the body, which are important risk factors for CVD. Obesity can also affect the development of asthma. A healthy diet and at least moderate activity can be protective against the negative effects of exposure to the environmental risk factors described in this chapter.

Characteristics of a healthy diet include low in saturated fat, low-moderate sodium, and high in fiber, fruit, and vegetables. It appears that focusing on changing only one or a couple of these factors is not enough to protect from CVD development and events, but rather the whole diet needs to be adjusted. The Mediterranean diet has been identified as particularly beneficial for preventing both CVD and asthma (Antó 2012; Dalen and Devries 2014; Garcia-Marcos et al. 2013; Nagel et al. 2010). The Mediterranean diet includes nuts, fruits, vegetables, green leafy vegetables, legumes, whole grain, fish, moderate alcohol, poultry, and olive oil. Many of these food groups have been found to decrease risk of cardiovascular and other diseases. Whole grains, fruit and vegetables contain fiber, vitamins, minerals, phenolic compounds, and other phytochemicals that may support the antioxidant response and reduce inflammation (Bhupathiraju and Tucker 2011; Lock et al. 2005; Tang et al. 2015). A high fiber diet may reduce insulin secretion, thus reducing the development of CVD related risk factors such as diabetes, dyslipidemia, and obesity (Bernstein et al. 2013; Ludwig et al. 1999). Fish, particularly oily fish, are high in omega-3 fatty acids (or *n*-fatty acids), a type of polyunsaturated fatty acid (PUFA) which have been found to be protective against CVD. There is some suggestive evidence that omega-3 fatty acids may also protect against decreased lung function and asthma (Romieu and Trenga 2001). Proposed mechanisms include the prevention of fatal arrhythmias, reduction of blood pressure, and reduction of inflammation (Breslow 2006).

Studies found that reducing total dietary fat was less effective at preventing CVD than reduction in specific types of fats, particularly saturated and *trans*-fatty acids. Reducing total fat intake may be beneficial for reducing serum cholesterol, but not for preventing cardiovascular events or death (Dalen and Devries 2014). On the other hand, mono- and poly-unsaturated fats have been associated with reduced risk of coronary events and deaths (Bhupathiraju and Tucker 2011). In a meta-analysis of 32 cohort studies examining the effects of mono-unsaturated fats on CVD, olive oil consumption showed the most consistent and significant protective effects, compared to total mono-unsaturated fats or the mono-unsaturated fat to saturated fat ratio (Schwingshackl and Hoffmann 2014). Other analyses found that replacing saturated fats with poly-unsaturated fats was better associated with reduced risk of coronary events and deaths than replacement with mono-unsaturated fats (Bhupathiraju and Tucker 2011). Mono-unsaturated fats can also include animal fats, therefore it is possible that plant-derived fats, olive oil in particular, may be more protective, or that olive oil use is a better indicator of a Mediterranean-style diet.

Interestingly, while the vitamins, minerals, beneficial fatty acids found in various foods are thought to be the bioactive compounds that have protective effects, supplementation trials have not shown as clear a benefit as dietary intake, with some trials showing protective effects, some with null results, and even some trials showing harmful effects at high doses of some supplements (Bhupathiraju and Tucker 2011; Myung et al. 2013). Therefore, interventions based on change in whole diet rather than supplementation are likely to be more protective.

Reducing sodium intake is also associated with a reduction in risk of high blood pressure and CVD, although the effect appears to follow a U-shape, where very low intake and high intake have been related to cardiovascular death and hospitalization (O'Donnell et al. 2015). An increase in potassium intake has also been associated with improved cardiovascular outcomes, with reductions in high sodium intake diets plus increase in potassium intake showing benefits.

The nutritional environment of the fetus has also been found to influence risk of disease, including CVD and asthma, in later life. Observations of surveys of men in England born in the early 1900s found that risk of death increased with lower birth-weight, head circumference, and ponderal index. Low growth rates and body weights up to the age of 1 year were associated with greater risk of development of CVD risk factors (e.g. blood pressure, plasma glucose and insulin, inflammatory biomarkers) and a higher risk of death from coronary heart disease. (Barker et al. 1993). Animal studies showed that poor fetal nutrition may affect structure and physiology of organs and tissues, including endocrine pancreas, liver, and blood vessels, thus leading to the effects seen later in life. Similar outcomes in terms of fetal nutrition and development of obesity, diabetes, and CVD in adulthood were also observed in children born during the Dutch famine (Painter et al. 2005; Roseboom et al. 2006).

2.2.3.6 Phthalates

Phthalates have been found to be asthma and allergy adjuvants, particularly DEHP and longer chain phthalates in *in vivo* studies. *In vitro* tests have found that eight-carbon phthalates, especially DEHP or MEHP induced rapid histamine production in the presence of a co-allergen (Jaakkola and Knight 2008). DEHP's interaction with PPAR receptors can modulate gene expression in tissues, and in mice, appears to increase lung air space and decrease the gas exchange surface (Miller and Marty 2010). The levels of exposure *in vivo* at which these effects were found, however, are much higher than typical human exposures.

Occupational studies where workers are exposed to heated PVC fumes, such as meat wrappers, have found an increased risk of reported asthma symptoms and decreases in lung function metrics (Jaakkola and Knight 2008). Studies of children have found a relationship between PVC in floors and wall materials with bronchial obstruction and wheeze, respiratory symptoms and infections. Dampness seems to increase the degradation of PVC flooring, and this degradation effect has been associated with asthma related symptoms in occupational settings and asthma and

rhinitis in children. These studies, however, did not measure phthalate exposure levels directly, either via environmental or biomarker samples. Several studies in Bulgaria, Sweden, and Taiwan did find an association between DEHP in house dust samples and allergy, asthma, rhinitis, and wheezing.

Exposure to higher molecular weight phthalates, such as DEHP, tend to be via ingestion food or dust, rather than inhalation (Wormuth et al. 2006). Dermal exposure is possible, but more likely to be via application of personal care products or wearing of gloves or textiles containing phthalates. Phthalate exposure is often multi-pathway, and measurement of urinary metabolites is a useful quantification of a marker of total exposure. It can be difficult to determine the contribution of various pathways and routes of exposure in the real world, as dust ingestion rates are highly uncertain for children and adults, and exposure via diet, dermal, and air are not well quantified. The most comprehensive examination of multi-pathway exposures was done by modelling exposures using a scenario based risk assessment approach (Wormuth et al. 2006), which demonstrated the potential contribution of various pathways to exposure for different age groups.

2.2.3.7 Cleaning Products

Occupational exposure to cleaning agents and disinfectants has been associated with asthma onset. The European Community Respiratory Health Survey II (ECRHS II) found the most significant risk of asthma onset in occupational settings was with use of cleaning products, particularly for nurses (Kogevinas et al. 2007). In Finland, a case-control study found a 42 % increase in risk for cleaning women compared to those in administrative types of jobs (Jaakkola and Jaakkola 2006; Zock et al. 2007). Asthma onset was also linked to use of spray cleaning products, including air fresheners, glass cleaners, and furniture cleaners, at least once a week in the general population. This risk was higher with use of multiple products. Quaternary ammonium compounds have been identified as sensitizers, and have been most strongly associated with occupational asthma, particularly in hospital settings (Heederik 2014).

Cleaning products contain a number of potentially irritating or sensitizing chemicals, which, when applied, lead to exposure, generally through inhalation, which would be the route of most relevance for asthma (Nazaroff and Weschler 2004). Another way in which cleaning products can lead to exposures to pollutants is via secondary reactions. Unsaturated organic compounds such as terpenes can form volatile organic compounds that may affect asthma in the presence of reactive substances such as ozone and the hydroxyl radical, or surfaces of walls or furniture (Nazaroff and Weschler 2004; Singer et al. 2006). Terpenes, for example, react with ozone and various surfaces to produce formaldehyde and other potentially airway irritating chemicals. Secondary organic aerosols can also form from reactions of volatile compounds released by cleaning products. These aerosols tend to be less than 2.5 μm in diameter and can persist at high levels for several hours post-production (Singer et al. 2006).

2.2.3.8 Dampness and Mould

In Europe, the proportion of the population living in homes with self-assessed problems of damp ranges from 10 to 50 % in the period of time between 1995 and 2001 (Heinrich 2011; WHO guidelines for indoor air quality n.d.). Dampness has been related to respiratory symptoms in various studies, although the means by which dampness has been measured has been quite variable (Kennedy and Grimes 2013). A meta-analysis of people living in damp or mouldy homes found a 30–50 % increase in risk of asthma (Fisk et al. 2007). In a meta-analysis of 8 European cohorts, exposure to dampness/mould at home in first 2 years of life resulted in an adjusted OR of early asthma symptoms of 1.39 (1.06–1.84) (Tischer et al. 2011).

Many studies use qualitative methods of assessing dampness and mould, such as questionnaire, visual assessment by trained assessor, dampness or mould index, or mould odour, especially near skirting of boards, which is area where moisture is most likely to accumulate over time and promote growth of micro-organisms, insects, rodents, release of chemicals from damp materials. Temperature and relative humidity have also been used as measures of indoor dampness. In recent times, however, quantitative measures of dampness and mould did not necessarily find any associations with health outcomes (Kennedy and Grimes 2013). Duration and period of exposure may also determine the health response (Heinrich 2011; Kennedy and Grimes 2013). Finally, it is difficult to know what particular hazard(s) from dampness is the explanatory variable, as many biological and chemical agents are released due to dampness or water damage.

2.2.3.9 Allergens

Allergic asthma phenotypes may be the largest group of asthma phenotypes, especially in childhood (Wenzel 2006). Common environmental triggers in homes include dust mite, cockroach, cat (and other pets) and mouse (Ahluwalia and Matsui 2011). Grass and tree pollens can also be triggers. Many biological and chemical agents have been demonstrated to be sensitizers in the workplace, leading to occupational asthma (List of substances that can cause occupational asthma—HSE n.d.). Removal of exposure usually stops symptoms, although for non-occupational triggers, it may be difficult to completely remove the sensitizing agent from an individual's environment. As asthmatics may be sensitized to more than one allergen, cleaning and pest management solutions in homes need to be multi-pronged and sustained in order to have an effect (Morgan et al. 2004).

2.2.3.10 Other Exposure Factors

Exposures are a product of environmental sources, conditions, and people's locations and activities. Reduction of exposures by modifying any of these factors improves health by improving symptoms and reducing risk of developing disease. Additionally, the "general external" sphere of the exposome has an impact on the "specific external"

factors described in this chapter. Improvements in “general external” factors not only directly impact health, but also affect “specific external” factors. For example, reduction of psychosocial stress can reduce the body’s general inflammation and also reduce risk of asthma exacerbations or heart attacks. Improvement of one’s home environment can not only reduce stress, but also reduce exposures to various pollutants.

Most exposure occurs indoors, and this consists of pollutants generated indoors and those that infiltrate indoors. Building materials, tightness, and ventilation, products used inside, and people’s activities are all predictors of exposure. Indoor microenvironments (including both buildings and vehicles) are sources of multiple chemicals and other environmental agents. Not including work, indoor exposures occur primarily at home. Time spent in other establishments, such as stores and restaurants, is generally of low duration and frequency (Loh et al. 2008). The indoor environment can be an important modifier of air pollutant exposures and related health effects. Air cleaners have been shown to be an effective reducer of some indoor pollutants (Barn et al. 2008) and the use of air conditioning, which tends to indicate newer buildings and lower infiltration of outdoor pollutants, was associated with a reduction in hospital admissions related to particulate matter (Janssen et al. 2002). The quality of the indoor environment can also have an effect. For example, poor housing stock can mean poor insulation, thus leading to poor indoor climate conditions such as low temperature and drafts, greater infiltration from air pollutants, noise, and dampness. Conversely, an overly well-insulated but poorly ventilated building can have a build-up of pollutants indoors and humidity, leading also to dampness indoors.

In transit exposures typically consist of pollution entering the vehicle from outdoors, or self-pollution from the vehicle. Although time spent in-transit is not necessarily a large part of a person’s day (~6 %), this microenvironment may contribute a much larger amount to a person’s exposure than the percentage of time spent in transit (~24 %) (de Nazelle et al. 2013). Mode of transport not only modifies a person’s air pollution exposure (McNabola et al. 2008; Zuurbier et al. 2010), but can also be a source of physical activity, thus reducing risk of obesity, an asthma and CVD risk factor.

2.3 Conclusion

Two of the most common types of diseases world-wide, cardiovascular diseases and asthma, are a complex interplay of genetics and environment. The environmental aspect of disease is itself a complex set of factors. Thinking holistically about disease using the concept of the exposome, developing methods for analysing the contribution of multiple factors, and understanding individuals’ circumstances broadly, can help us better intervene to reduce disease risk. This chapter has addressed several aspects of the “specific external” sphere of the exposome, as originally defined by Wild (2012). Although it is not an exhaustive review of environmental causes of cardiovascular disease and asthma, it already shows how many factors contribute to the development and manifestation of disease.

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