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REVIEW ARTICLE

Health effects of particulate air pollution: A review of epidemiological evidence

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Health effects of air pollution

Everyone is exposed to ambient air pollution every day, some to a more and some to a lesser extent. When the first scientist examined the effect of air pollution on health after the Meuse Valley fog in 1930 (Firket, 1936) or the London smog in 1952 (Ministry of health, 1954), no one could have known what an extended field of research they started.

Today, a lot of research is done on various aspects of air pollution. As shown in Figure 1, human health can be affected in all stages of life—from conception to old age. This review seeks to give an overview on the variety of health risks air pollution poses with a focus on epidemiological studies. Due to the vastness of the field, this review cannot go into too much detail in each section. However, it will give the reader a comprehensive impression on the large number of health effects of air pollution. Where available, the authors refer to existing reviews that might offer more depth in a certain field for the interested reader.

The first six sections deal with different health outcomes in respect to ambient air pollution. Section 7 explains potential mechanisms that may lead from the inhalation of particles to adverse health outcomes. The last section finally gives an overview on research gaps that exist in the field and possible directions that research might take.

1. Air pollution and mortality

Mortality is the most studied health endpoint in association with air pollution. One reason is the widespread availability of mortality data for large populations and another reason is the importance of mortality in estimating health impacts. Studies have been conducted on all-natural cause and cause-specific mortality such as cardiovascular and pulmonary mortality. Studies have addressed the impact of acute and chronic exposures. Studies investigating acute or short-term effects are based on day-to-day changes in exposure, whereas those examining chronic effects are based on long-term cumulative exposure to air pollution. Table 1 provides an overview indicating the number of published short-term and long-term studies.

1.1. Short-term studies

Short-term studies, usually time-series or case-crossover studies, explore associations between short-term changes in air pollution exposure and daily death counts (Brook et al., 2010; Pope & Dockery, 2006). There is a large amount of time-series studies on air pollution effects using particulate matter (PM) with an aerodynamic diameter <10 μm (PM_{10}) and/or <2.5 μm ($PM_{2.5}$) as exposure pollutants. In the United States, for example, the "National Morbidity, Mortality and Air Pollution Study" (NMMAPS) originally conducted in 20 and later in 90 of the largest cities and metropolitan areas from 1987 to 1994 reported small, but constant positive associations between PM_{10} and death (Samet et al., 2000). These findings were confirmed in several re-analyses (Dominici et al., 2003; Dominici et al., 2005; Health Effects Institute, 2003). Current criteria for air pollution guidelines are based on these studies. For Europe, the most important and extensive studies

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Abbreviations
ACS, American Cancer Society;
AD, Alzheimer's disease;
AMI, acute myocardial infarction;
APHEA, air pollution and health effects—a European approach;
APHENA, air pollution and health: a European and North American approach;
BC, black carbon;
BP, blood pressure;
BS, black smoke;
CD40L, CD40 Ligand;
CNS, central nervous system;
CO, carbon monoxide;
COPD, chronic obstructive pulmonary disease;
CRP, C-reactive protein;
CVD, cardiovascular diseases;
EC, elemental carbon;
ECG, electrocardiogram;
EPA, environmental protection agency;
FVII, Factor VII;
FEF_{25-75}, forced expiratory flow at 25–75% of vital capacity;
FEV_1, forced expiratory volume in 1 second;
FMD, flow-mediated dilatation;
FVC, forced vital capacity;
GIS, geographic information systems;
HEI, Health Effects Institute;
HF, high frequency domain;
HRV, heart rate variability;
HS, high sensitivity;
IL-6, interleukin-6;
IUGR, intrauterine growth retardation;
LBW, low birth weight;
LF, low frequency domain;
LUR, land use regression;
MI, myocardial infarction;
NMMAPS, National Morbidity, Mortality and Air Pollution Study;
NO, nitric oxide;
NO_2, Nitrogen dioxide;
OC, organic carbon;
PAH, polycyclic aromatic hydrocarbons;
PD, Parkinson's disease;
PEF, peak expiratory flow;
PM, particulate matter;
PM_{10}, particulate matter with an aerodynamic diameter <10 μm;
$PM_{2.5}$, particulate matter with an aerodynamic diameter <2.5 μm;
PNC, particle number concentration;
QTc, corrected QT interval;
RMSSD, root mean square of successive normal-to-normal interval differences;
ROS, reactive oxygen species;
SAA, Serum amyloid A;
SDNN, standard deviation of all normal-to-normal intervals;
SES, socioeconomic status;
SGA, small for gestational age;
sICAM, soluble inter-cellular adhesion molecule 1;
SSV, statistical search variable;
sVCAM-1, soluble vascular cell adhesion molecule 1;
TF, tissue factor;
TNF α, tumor necrosis factor α;
TSP, total suspended particles;
UFP, ultrafine particles, particles <100 nm;
vWF, Von Willebrand factor;
WHO, World Health Organisation;

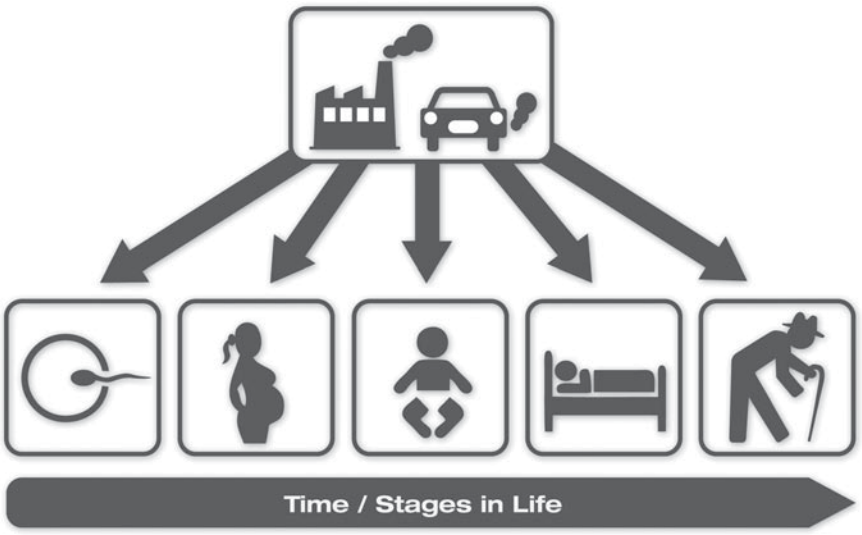

Figure 1. Stages in life of special susceptibility toward air pollution.

are the "Air Pollution and Health Effects—a European Approach" (APHEA and APHEA2) projects (Analitis et al., 2006; Katsouyanni et al., 1995; Katsouyanni et al., 1996; Katsouyanni et al., 1997; Katsouyanni et al., 2001), which showed small but significant associations for all-cause, cardiovascular and respiratory deaths with PM_{10} and also black smoke (BS) (Samoli et al., 2005). More recently, the APHENA (Air Pollution and Health: a European and North American Approach) sought to provide an understanding of the degree of consistency among findings of multi-city time-series studies on the effect of air pollution and mortality by analyzing data from APHEA, NMMAPS and 12 Canadian cities in a combined approach. The results were relatively robust to the underlying analysis approach and quite similar to the initial independent analyses. PM_{10} effects on

mortality were close for APHEA and NMMAPS, while the associations for the Canadian studies were higher (Samoli et al., 2008).

Short-term studies on particle number concentrations (PNC) of particles <100 nm, also referred to as ultrafine particles (UFP), and mortality are still rare (Tables 1 and 2). One of the first short-term studies on UFP and mortality was published by Wichmann et al. in 2000 (2000). They analyzed all-cause, cardiovascular, and respiratory mortality in Erfurt, Germany, a city of about

Table 1. Air pollutants and health outcomes.

	Short-term studies						Long-term studies					
Variables	PM_{10}	$PM_{2.5}$	UFP	BS/BC	EC/OC	Other	PM_{10}	$PM_{2.5}$	UFP	BS/BC	EC/OC	Other
Mortality												
All cause	xxx	xxx	x	x	x		xx	xx	x	xx	x	x
Cardiovascular	xxx	xxx	x	x	x		xx	xx	x	xx	x	x
Pulmonary	xxx	xxx	x	x	x		xx	xx	x	xx	x	x
Pulmonary effects												
Lung function, e.g., PEF	xxx	xxx	xx		x		xxx	xxx				
Lung function growth							xxx	xxx				
Asthma and COPD exacerbation						x						
Acute respiratory symptoms		xx	x			x	xxx	xxx				
Medication use			x									
Lung cancer												
Hospital admission							xx	xx	x			x
Cardiovascular effects												
Hospital admission	xxx	xxx					x	x				x
ECG-related endpoints												
Autonomic nervous system	xxx	xxx	xx	x								
Myocardial substrate and vulnerability		xx	x	x		x						
Vascular function												
Blood pressure	xx	xxx	x	x	x	x						
Endothelial function	x	xx	x	x		x						
Variables	PM_{10}	$PM_{2.5}$	UFP	BS/BC	EC/OC	Other						
Blood markers												
Pro inflammatory mediators	xx	xx	xx	x	x	xx						
Coagulation blood markers	xx	xx	xx	x	x	x						
Endothelial function	x	x	xx	x	x	x						
Reproduction												
Premature birth	x	x				x						
Birth weight	xx	x				xx						
IUR/SGA	x	x				x						
Fetal growth						x						
Birth defects	x					x						
Infant mortality	xx	x				xx						
Sperm quality	x	x				x						
Neurotoxic effects												
Diseases of the central nervous system				x		xx						

x, few studies; xx, many studies; xxx, large number of studies.

Table 2. Short-term studies on selected air pollutants and mortality.

Variables	UFP/PNC	BS/BC	EC/OC
All cause	Wichmann 2000↑	Samoli et al. 2005↑	Ostro et al. 2007–
	Stölzel et al. 2007↑		
	Breitner et al. 2009↑		
Cardiovascular	Wichmann 2000↑	Samoli et al. 2005↑	Ostro et al. 2007↑
	Forastiere et al. 2005↑		Ostro et al. 2008↑
	Stölzel et al. 2007↑		
Respiratory		Samoli et al. 2005↑	Ostro et al. 2007–
Cardio-respiratory	Stölzel et al. 2007↑		

↑positive association.
–no association.

200,000 inhabitants from September 1995 to December 1998. They found that both fine and UFP showed independent effects on mortality. Results suggested a more delayed association for UFP than for fine particles and the overall association was slightly stronger for respiratory diseases than for cardiovascular diseases (cvd) when cause-specific mortality was analyzed. A few years later, Stölzel and colleagues (2007) re-analyzed the data using an extended dataset (September 1995 to August 2001) as well as an alternative modeling approach similar to the APHEA2 study (Touloumi et al., 2004). They also found a small increase in total and cardio-respiratory mortality in association with different size ranges of UFP for a lag of 4 days. In contrast to the first study in Erfurt, they did not see associations for fine particle mass with total or cause-specific mortality. A recent reanalysis by Breitner et al. (2009), moreover, evaluated changes in the association between daily mortality and UFP, as air quality substantially improved during the study period. Overall, relative risk estimates were consistent, but somewhat smaller than that in the previous analyses. Results further suggested that the relative risks for short-term associations of UFP decreased as pollution control measures were implemented in Eastern Germany. In addition to the German study, results from a case-crossover study in Rome indicate an association between fatal coronary events and PNC, a proxy for UFP, PM_{10} and carbon monoxide (CO), which appeared strongest for the age group above 65 (Forastiere et al., 2005).

The few studies considering the associations between mortality and elemental and organic carbon indicate a positive association, especially for low educated people (Ostro et al., 2006; Ostro et al., 2008).

In this context, it is important to note that the terms elemental carbon (EC), black carbon (BC), BS or "soot" have been widely interchanged in the literature in the past. The reason for this could be the similarity of all those carbonaceous aerosol fractions. They are supposed to be comparable, but nevertheless have slightly different thermal, optical, and chemical behavior in most cases. Therefore, there is an effort in the community, to use these terms more precisely (Andreae and Gelencser, 2006; Schauer, 2003).

BS measurements were the earliest systematic measurements of particulate air pollution in the United Kingdom, and the method has been used in many European countries (Hoek et al., 2002). Air is sampled through a filter and the darkness of the stain, measured by optical reflectance, and is converted to a Black Smoke Index, given in units of mg m^{-3}. The conversion was established in the United Kingdom in the 1960s based on domestic coal smoke emissions. It has remained the same while the quantity and composition of the PM have changed greatly, notably as coal burning in cities has declined so that the interpretation as a total mass concentration is no longer valid.

The term "black" carbon implies that this component is responsible for the absorption of visible light and is generally used when optical methods are applied for its determination (e.g., optical transmission method, known as aethalometry). The relationship between BS and BC measurements was described by Quincey (Quincey, 2007; Quincey et al., 2011).

"EC" is conventionally the preferred term in conjunction with thermal and wet chemical determinations by carbon analyzers. Multiple methods exist for measuring the EC content of particles, which may yield substantially different concentrations (Schmid et al., 2001). While the total carbon (TC) content corresponds well to most analytical approaches, differences of a factor of two have been reported for EC when comparing the two most commonly applied analytical protocols, NIOSH (National Institute of Occupational Safety and Health) method 5040 and IMPROVE (Interagency Monitoring of Protected Visual Environments) (Chow et al., 2001; Schmid et al., 2001). This discussion on EC is directly linked to OC since for simplicity OC is generally defined as the difference between TC and the sum of elemental and inorganic carbon. The influence of the measurement method on EC/OC concentrations should be kept in mind when comparing different studies investigating the effects of EC and OC on human health.

It is important to recognize that strong relationships between BC and EC have been observed given consistent measurement techniques and relatively constant EC sources (Babich et al., 2000; Ballach et al., 2001; Lavanchy et al., 1999), but these relationships are dependent on the BC and EC method, as well as the sources of EC (Borak et al., 2003; Cyrys et al., 2003).

1.2. Long-term studies

Long-term studies compare mortality across populations that vary in their long-term exposure to air pollution usually using a cohort design. The Harvard Six Cities Study (Dockery et al., 1993; Laden et al., 2006) and the American Cancer Society (ACS) Study (Pope et al., 1995; Pope et al., 2002), first published in the mid 1990s, are considered among the important studies in this field. They show a clear increase in all-cause, but especially in cardiovascular/cardiopulmonary mortality in association with $PM_{2.5}$. The extended reanalysis of the Harvard Six Cities Study by Laden et al. (2006) also shows that an overall reduction in $PM_{2.5}$ levels over the years resulted in reduced long-term risk for deaths due to cardiovascular and respiratory disease.

The first large European cohort study of mortality and air pollution was conducted in the Netherlands. The authors found evidence of increased risks for all-cause and cardiopulmonary mortality for those living close to a major road (Hoek et al., 2002). An extended analysis of the same cohort showed somewhat smaller effect estimates which were significant only for all-cause and respiratory mortality (Beelen et al., 2008). A study in German women reported small but significant increases in cardiopulmonary mortality for women living within 50 meters of a major road, with nitrogen dioxide (NO_2)

and PM_{10} (Gehring et al., 2006). Some authors examined BS as exposure variable (Table 3) and found positive but not always significant associations (Beelen et al., 2008; Brunekreef et al., 2009; Elliott et al., 2007; Filleul et al., 2005; Hoek et al., 2002; Le Tertre et al., 2002; Pekkanen et al., 2000; Poloniecki et al., 1997; Samoli et al., 2005).

To date, there are no long-term studies examining UFP and mortality as can be seen in the overviews Brook et al. (2010) give in their extensive review on PM and cvd.

1.3. Susceptible subgroups

Some studies have identified individuals with diabetes as a subgroup which is more susceptible to the adverse effects of particulate air pollution than the general population (Zanobetti and Schwartz, 2001; Zeka et al., 2006). Furthermore, studies also suggested a stronger effect in myocardial infarction (MI) survivors (Bateson and Schwartz, 2004). von Klot et al. (2009) investigated the long-term effects of traffic-related air pollution on mortality in a cohort study of MI survivors in Worcester, MA, USA. They found an increase in mortality after the second year of survival in association with chronic traffic pollution at the participants' home addresses. In a European short-term study in five European cities, Berglind et al. (2009) found that exposure to traffic-related air pollution was associated with daily mortality in MI survivors. Moreover, the elderly and those with a lower socioeconomic status (SES) have been identified to be especially susceptible to particulate air pollutants (Forastiere et al., 2005; Forastiere et al., 2007; Ostro et al., 2006).

1.4. Conclusion

The various long- and short-term studies on mortality and $PM_{10}/PM_{2.5}$ have been summarized in a number of reviews and quantitative meta-analyses, and all authors conclude that there is clear evidence for a positive association (Brook, 2007; Brook, 2008; Pope, 2007; Pope and

Table 3. Studies on black smoke.

First author, year,	Country	Time period	BS level (μg/m³)	Outcome	Association
Mortality, short-term studies					
Samoli et al., 2005, 284	15 cities in Europe (APHEA)	1990–96 1992–96	50th, 90th percentile highest: 64, 122 (Athens) lowest: 10, 26 (Dublin)	All-cause and cause-specific mortality	Positive linear association
Mortality, long-term studies					
Brunekreef et al., 2009, 44 (HEI Report)	Netherlands	1987–96	Min, mean, max Backgr.: 9, 14, 19 Backgr. + local: 9, 17, 35	All-cause and cause-specific mortality	Positive for all-cause mortality No association for cause-specific mortality
Beelen et al., 2008, 22	Netherlands	1987–96	Min, mean, max Backgr.: 8.7, 13.9, 19.5 Overall: 8.7, 16.5, 35.8	All-cause and cause-specific mortality	Positive but n.s.
Elliott et al., 2007, 86	UK	1966–70 1990–94	Mean (sd) 74.9 (44.7) 13.3 (5.3)	All-cause and cause-specific mortality	Positive for all-cause, cardiovascular, cardiorespiratory, respiratory mortality
Filleul et al., 2005, 90	France	1974–76 1978–81 1990–97	Mean 28 (Rouen) – 152 (Marseille) 19.9–43.2 (both Bordeaux) 9.8 (Rouen) – 14.4 (Lille)	All-cause and cardiopulmonary mortality	Positive for all-cause, n.s. for cardiopulmonary mortality
Hoek et al., 2002, 141	Netherlands	1986–94	Min, mean, max Backgr.: 9.6, 15.1, 21.6 Backgr.+local: 9.6, 15.1, 35.8	All-cause and cause-specific mortality	Positive for cardiopulmonary mortality
Hospital admission					
Le Tertre et al., 2002, 183	5 European cities	1992–96	Mean (sd) Lowest: 12.5 (11.3) (Netherlands) Highest: 38.7 (14.0) (Barcelona)	Hospital admission for cardiac and ischemic heart disease	Mostly positive, especially >65y
Poloniecki et al., 1997, 246	UK	1987–94	Min: 1 Median: 12 Max: 62	Cardiovascular hospital admission	Significant association for circulatory diseases, angina and acute myocardial infarction.
Blood markers					
Pekkanen et al., 2000, 232	UK	1991–93	Median: 13.0 Mean: 15.4 Max: 88.8	Plasma fibrinogen	Positive association only in the warm season

Dockery, 2006; Ren and Tong, 2008). Anderson (2009) remarks in his review that the consistency in studies examining PM_{10} and cardiovascular mortality is remarkable with most of the estimates showing a positive association. UFP and other markers of air pollution, however, have not been extensively studied, and although data also indicate a positive association, more research is needed.

2. Air pollution and pulmonary effects

Intuitively, the lung seems to be an obvious organ to be affected by air pollution. Hence, the body of literature on associations between air pollution and lung function is vast, with a large variety of measured outcomes. Table 1 gives an overview over the most commonly measured parameters and air pollutants. A number of reviews summarize the available literature, mainly for PM_{10} and $PM_{2.5}$.

2.1. Reviews–children

There are many studies on respiratory effects of air pollution in children, as children are more vulnerable to harmful effects of air pollution than adults because their lungs are immature (Heinrich and Slama, 2007) and their defense mechanisms are still evolving (Finkelstein and Johnston, 2004; Salvi, 2007). Moreover, children have a higher-minute ventilation, involve more in vigorous activities, and spend more time outdoors than adults (Buka et al., 2006). Lung function in childhood is a strong predictor for lung function in adulthood and therefore an important health predictor (Heinrich and Slama, 2007). Results of the Californian Children's Health Study, for example, showed that children growing up in the most polluted areas were left with substantial deficits in lung function at age 18 (Gauderman et al., 2004). Künzli et al. (2001) found that functional deficits remain until adulthood.

Short-term studies

Ward and Ayres (2004) reviewed short-term studies in children on lung function measurements like peak expiratory flow (PEF) and lower respiratory symptoms or coughs. They found that the majority of studies indicate an adverse effect of particulate air pollution which is greater for $PM_{2.5}$ than for PM_{10}. However, they also noted that the reviewed studies show heterogeneity and that there is also evidence of publication bias. Schwartz (Schwartz, 2004) pointed out a series of summer camp studies in his review, where children were exposed almost all day long due to the living conditions at the camp. These studies showed a decline in lung function during air pollution episodes. A very striking example was given by Pope (1989) who examined hospital admissions of children in the Utah valley during three consecutive winters. These winters were before, during and after a strike that closed down a local steel mill, the largest source of wintertime air pollution. The drop in hospital admission for asthma and pneumonia in children was more than 50% during the closure of the steel mill. Heinrich and Slama (2007) listed a number of short-term studies that found associations between fine PM and lung function development as well as respiratory symptoms. The results of these short-term studies are mostly in line with results of a few long-term studies on effects of fine PM on lung function in children (see next paragraph).

Studies on susceptibility showed that children with asthma symptoms are more susceptible to air pollutants than healthy children and therefore many studies have focused on asthmatic children (Heinrich and Slama, 2007; Schwartz, 2004).

Long-term studies

A recent review by Bråbäck and Forsberg (2009) concentrated on the effects of traffic-related pollutants in prospective cohort studies in children. The authors concluded that the consistency of the published results indicate that traffic exhaust contributes to the development of respiratory symptoms in healthy children, while the role of air pollution exposure in the development of allergic sensitization is less clear. Schwartz (2004) concluded in his review that "the overwhelming weight of the recent evidence suggests that traffic pollution is associated with the risk of developing asthma".

In general, reviews agree that there is a clear adverse association between ambient air pollution and lung function, lung development and respiratory symptoms in children. Several studies also showed a reduction in respiratory symptoms (Avol et al., 2001; Bayer-Oglesby et al., 2005; Friedman et al., 2001; Heinrich et al., 2002), asthma-related hospital admissions and emergency room visits (Friedman et al., 2001) and an attenuation in lung function decline (Downs et al., 2007) after improvements in air quality.

2.2. Reviews-adults

There are only a limited number of reviews on adults, as the majority of studies examine children and adolescents. A review by Götschi et al. (2008) examining studies of long-term effects of air pollution on lung function, found that 37 out of 58 reviewed publications investigated children. For adults, the reviewed cross-sectional and longitudinal studies showed a trend toward a negative association for lung function and air pollutants. The authors concluded, especially with the evidence from larger studies, that lung function levels in adults correlate with air pollution exposure. However, air pollution measures and respiratory outcomes vary between the studies, making a quantitative comparison impossible. Pope and Dockery (Pope and Dockery, 2006) concluded in their extensive review on the health effects of fine particulate air pollution that long-term exposure to PM is associated with deficits in lung function and increased symptoms of obstructive airway disease. They also pointed out that air pollution exposure is not only associated with respiratory morbidity and mortality, but that the systemic inflammation associated with chronic obstructive pulmonary

disease (COPD) contributes to cardiovascular risk and that COPD itself is a risk factor for cardiovascular morbidity and mortality, independent of other risk factors.

2.3. Single studies–UFP

The number of epidemiological studies on UFP is still relatively small, and they are usually not or only briefly covered in reviews.

One of the first studies examining the association between UFP and respiratory health in a group of adult asthmatics was published by Peters et al. (1997b). Participants kept a symptom diary and measured PEF daily for a period of 6 months. Air pollution was measured daily at a fixed monitoring site using mass concentrations and number concentrations in three size ranges, namely 0.01 μm ≤ d <0.1 μm, 0.1 μm ≤ d < 0.5 μm and 0.5 μm ≤ d < 2.5 μm. The authors found small but consistent associations between elevated particles in all size ranges below 0.5 μm for mass and number concentrations and a decrease in PEF. Associations for PEF were most pronounced for the fraction of 0.01–2.5 μm for the number concentrations. In addition, an increase in coughs, and feeling ill during the day was seen for several of the measured size ranges. Analogue results for PEF were seen in a similar Finnish study (Penttinen et al., 2001); however, no associations were observed with respiratory symptoms or medication use. Another panel study on adult asthmatics in Germany using similar size fractions to Peters et al. (1997), on the other hand, showed that an increase in particles was associated with use of ß$_2$-agonists (all size ranges for number concentrations as well as mass concentrations <2.5 μm) and corticosteroids (all measured size ranges for number and mass concentrations) (Klot et al., 2002).

A more recent study in London, England, compared several lung function parameters in adults with mild or moderate asthma walking along Oxford Street, a busy shopping street with a lot of diesel-powered bus and taxi traffic, and walking in a nearby park. They found that reductions in the forced expiratory volume in 1 s (FEV_1), forced vital capacity, forced expiratory flow at 25–75% of vital capacity (FEF_{25-75}) and exhaled breath condensate pH were associated with UFP exposure at most measured time points, while there were no consistent associations for $PM_{2.5}$ (McCreanor et al., 2007). A study in the Netherlands, on the other hand, found only weak associations between various measures of lung function and PNC 6 h after exposure in healthy adults; however, the number of participants was only small (Strak et al., 2009). Another study in four European cities also found no consistent associations between lung function and 24-h average particle number or particle mass concentrations measured indoor and outdoor at the participants' homes as well as at a fixed measurement site (de Hartog et al., 2009a). A limited ability to assess lagged effects over several days could be one explanation for the missing association as most other studies report lagged effects. However, a study from Taiwan in asthmatic children also found no significant associations for the PEF rate and different measures of air pollutants from personal measurements or a fixed monitoring site (Tang et al., 2007). Most studies on UFP particles and respiratory diseases are panel studies, and only one study on hospital admission for respiratory diseases has been carried out so far (Andersen et al., 2008). This study, conducted in Copenhagen, Denmark, extracted daily counts of hospital admissions for respiratory diseases in the elderly (≥65 years) and asthmatic children (5–18 years) for 3.5 years and associated the daily counts with air pollution data from a central monitoring site. They found significant associations between hospital admission for respiratory diseases and total number concentrations of particles 6–700 nm in diameter; however, associations diminished after additional adjustment for PM_{10} or $PM_{2.5}$. The study did not see any association for total number concentrations of particles 6–700 nm in diameter and pediatric asthma, and only a weak association for pediatric asthma and particles with a median diameter of 212 nm. Detailed analyses showed, however, that the number concentration in the ultrafine size ranges especially showed a large spatial variation. As only data from one urban background monitor was used for the analyses, exposure misclassification cannot be excluded.

Taken together, the few epidemiological studies conducted on effects of UFP indicate an adverse relationship on respiratory outcomes; however, results are not consistent.

2.4. Single studies–other markers of air pollution

In addition to the most common markers for air pollution, few studies examine other markers such as the coarse fraction of particles, usually defined and measured as particles between 2.5 μm and 10.0 μm. A review comparing epidemiological studies on health effects of coarse and fine particles found that the coarse fraction was a better predictor of the daily number of hospital admissions in several studies on asthma, COPD and/or all respiratory admissions than fine particles. However, the number of studies in the review was small as only studies reporting effect estimates for both particle fractions were included (Brunekreef and Forsberg, 2005).

McCreanor et al. (2007) also looked at EC in the abovementioned study in London. Results were very similar to those for UFP, i.e. they found reductions in lung function measures with higher levels of EC.

A study by Heinrich et al. (2005) used traffic intensity estimated from residential street type as exposure parameter in a cross-sectional study in almost 7000 German adults. They found that living on extremely or considerably busy roads was associated with chronic bronchitis. Positive but not statistically significant associations were seen for nocturnal coughing attacks, wheeze during the past 12 months and hay fever, while no increases were seen for asthma. In contrast to this, a study in Swedish adults (Lindgren et al., 2009) reported an association

between asthma and COPD diagnosis and symptoms of asthma or chronic bronchitis and living within 100 meters of a road with >10 cars per minute. Moreover, self-reported traffic exposure was associated with asthma symptoms, diagnosis of asthma and diagnosis of COPD. Results of the SAPALDIA studies provide evidence for adverse events of traffic exposures on respiratory health. The authors concluded that living close to main streets increases the risk for certain respiratory symptoms in adults (Bayer-Oglesby et al., 2006). A hospital-based longitudinal study in Californian children demonstrated that living within 300 meters of a major road increased the risk of hospital encounters in asthmatic children up to 18 years of age (Chang et al., 2009). More recent analyses of The California Children's Health Study also showed that new-onset asthma is associated with traffic-related pollution near homes and schools (McConnell et al., 2010).

2.5. Susceptible subgroups

As described above, children have been shown to be more vulnerable to ambient air pollution than adults. Moreover, patients with underlying diseases, such as asthma, seem to be more susceptible.

2.6. Lung cancer

As part of the American Cancer Prevention Study II, risk factors for about 500,000 adults were linked with long-term exposure to air pollution and combined with vital status and cause of death. Data showed that a 10 μg/m^3 elevation in $PM_{2.5}$ was associated with an 8% increase in lung cancer mortality even after adjustment for known risk factors such as smoking or occupational exposure (Pope et al., 2002). Associations between lung cancer mortality and air pollution have also been demonstrated in the Harvard Six-Cities Study (Dockery et al., 1993).

2.7. Conclusion

Overall, the vast majority of published studies indicate an association between air pollution and adverse respiratory outcomes, in healthy as well as in diseased populations. The main focus is on respiratory health of children. While the body of literature on PM_{10} and $PM_{2.5}$ is large, the number of studies using UFP is still comparatively small. Due to the large variety of outcomes and study types, a comparison of effect estimates is often difficult.

3. Air pollution and cardiovascular effects

Although it may intuitively seem that PM would pose a health risk mostly to the lungs, evidence indicates that the highest attributable risk of adverse health effects of PM is upon the cardiovascular system. In 2010, the American Heart Association concluded in an updated Scientific Statement, that "a wide array of new studies that range from epidemiology to molecular and toxicological experiments have provided additional persuasive evidence that present-day levels of air pollutants contribute to cardiovascular morbidity and mortality" (Brook et al., 2010; Brook et al., 2004).

Studies on associations between air pollution and cardiovascular mortality have been covered in section 1 of this review. There is also a variety of blood markers, for example fibrinogen and C-reactive protein (CRP), that are regarded as prognostic markers for cardiovascular risk. Increased levels of these blood markers have been found in association with air pollutants and more details can be found in section 4 of this review.

In addition, there are a large number of publications on associations between air pollution and hospital admission for cvd, atherosclerotic and ischemic events, or other markers indicating a decline in cardiovascular health such as heart rate variability (HRV), repolarisation changes, ST-segment depression or arrhythmia.

3.1. Hospital admission

Similar to mortality studies, studies on hospital admissions for cvd can be divided into short-term and long-term studies.

Short-term studies

Most of the published studies on air pollution and hospital admission for cvd are short-term studies. Brook et al. (2010) mention seven multi-city studies on cardiovascular hospital admissions and air pollution in their review on air pollution and cvd as well as one meta-analysis. All of them indicate a positive association between an increase of PM_{10} and cardiovascular hospital admissions. The estimates vary between a 0.8% (95% confidence interval: 0.6; 1.0) and 2.6% (95% confidence interval: 2.0; 3.0) increase in hospital admissions for an increment in PM_{10} of 20 μg/m^3. Pope and Dockery (2006) reach the same conclusion by comparing meta-analyses on air pollution and the risk of cvd hospital admissions. In addition to PM_{10}, their study results indicate a positive association for $PM_{2.5}$. The authors conclude that fine particulate pollution is principally responsible for the cardiovascular hospitalizations.

Moreover, they sum up the studies on hospitalization for stroke and stroke mortality that have been carried out concluding that there is a positive association (Pope and Dockery, 2006). When analyzed by stroke type, ischemic but not hemorrhagic stroke was associated with various air pollution parameters in different studies (Brook et al., 2010). A systematic review on air pollution and MI identified 19 studies on short-term effects of air pollution (Bhaskaran et al., 2009). The authors concluded that while associations with PM_{10} were limited, increasing daily $PM_{2.5}$ levels were commonly associated with increasing risk up to 2 days later. Results for gaseous pollutants, on the other hand, were mixed.

Long-term studies

The number of publications of long-term exposure to air pollution and cardiovascular hospital admission is limited. In their systematic review, Bhaskaran et al.

(2009) found that out of 26 only seven studies examined long-term associations between air pollution and MI. Overall, they concluded that evidence from long-term studies is still limited, possibly due to the small number of studies but also due to the small number of outcomes in prospective studies. Tonne et al. (2007) investigated the relationship between long-term exposure to traffic and the occurrence of acute myocardial infarction (AMI) in a case-control study. They observed a significant increase in the odds of experiencing an AMI with increasing exposure to traffic within 100 m of the subjects' residence and with living near major roadways. Zanobetti and Schwartz (2007) found that long-term exposure to PM_{10} was significantly associated with hospitalization for congestive heart failure and a new hospitalization for MI in patients who had survived an MI. Results from the Nurses' Health Study, however, showed no statistically significant association between nonfatal MI and PM_{10} exposure, while results for all-cause mortality and fatal coronary heart disease demonstrated a stable positive association in the same dataset (Puett et al., 2008). Miller et al. (2007) found in a prospective cohort study on more than 65,000 postmenopausal women that increased concentrations of $PM_{2.5}$ were associated with an increased risk of fatal and nonfatal first cardiovascular events.

To examine the impact of air pollution, an increasing number of studies use parameters which reflect subclinical physiological responses possibly related to the risk of cvd rather than comparatively rare severe events such as MI or death. Air pollution may influence different elements of heart function: Autonomic nervous system, myocardial substrate and myocardial vulnerability. These three components form the so-called "cardiac death triangle" (Zareba et al., 2001). An imbalance in the autonomic nervous system is for example reflected by changes in HRV. Changes in the myocardial substrate comprise myocardial injury, ischemia or hypertrophy. These may lead to increased morbidity and, subsequently, to fatal cardiac events. Myocardial vulnerability reflects the concept that some people are more likely to experience adverse outcomes such as cardiac arrhythmias or transient ischemia. All three components can be measured by an electrocardiogram and have been shown to be adversely impacted by ambient air pollutants as described later in this section.

3.2. ECG-related endpoints

Most of the commonly used parameters reflecting subclinical risk factors can be measured with an ECG. Zareba et al. (2001) divided them into three groups, according to the cardiac death triangle, as described above.

Autonomic nervous system

The autonomic nervous system continuously controls the performance of the entire cardiovascular system. Autonomic imbalance is a major contributor to the triggering of cardiac arrhythmias and, as a consequence, to the incidence of sudden cardiac death (Singer, 1995). Primarily reduced but also increased HRV has long been recognized as a marker for cardiac mortality in high risk or elderly populations (de Bruyne et al., 1999; Task Force, 1996; Tsuji et al., 1994). Additionally, it has been shown that HRV from 24-h recordings was a stronger predictor of death due to chronic heart failure than other conventional clinical measurements (Nolan et al., 1998). A recent systematic literature search and meta-analysis in 21 studies found that a low standard deviation of all normal-to-normal intervals (SDNN) after MI was associated with adverse outcomes such as mortality or significant cardiac complications (Buccelletti et al., 2009).

Several epidemiological studies on air pollution have used this noninvasive method to examine associations between short-term changes in air pollutant concentrations and cardiac health. Most studies found a decrease in HRV parameters in association with different ambient air pollutants, supporting the idea that ambient air pollution might disturb the autonomic function (Gold et al., 2000; Pope et al., 2004b; Schneider et al., 2010; Schwartz et al., 2005). Usually, one or more central measurement sites are used for air pollution exposure assessment and only few studies examined personal exposure to air pollution and HRV. Sullivan et al. (2005) measured inside the participants' homes in addition to outside exposure measurements, but found no associations between inside $PM_{2.5}$ and HRV. de Hartog et al. (2009b) found no association between HRV and personal, indoor or outdoor $PM_{2.5}$ 24 h after exposure in a panel of coronary heart disease patients. However, outdoor levels at 2- and 3-day lags were associated with decreased HRV in the subgroup of patients without intake of beta-blockers. Unfortunately, personal and indoor measurements were only available for the 24 h before the clinical visit, and 2- or 3-day lags therefore could not be analyzed for personal and indoor $PM_{2.5}$ in this study. A study in Pennsylvania, USA, on the other hand found acute changes in HRV parameters. SDNN and power in the low frequency domain (LF) and the high frequency domain (HF) decreased within 6 h after elevated personally measured $PM_{2.5}$ (He et al., 2010).

Brook (2010) and Pope and Dockery (2006) concluded that there is a general pattern across the large number of studies on heart rate and HRV indicating an adverse relationship to particulate air pollution, although the results are not entirely consistent (Wheeler et al., 2006).

Myocardial substrate and myocardial vulnerability

ST-segment depression during an exercise test is considered a reliable marker for myocardial ischemia among subjects with coronary heart disease (Zareba et al., 2001) and was investigated in association with air pollution in a variety of studies (Chuang et al., 2008; Gold et al., 2005; Lanki et al., 2008; Mills et al., 2007; Pekkanen et al., 2002). In addition, many other markers of adverse physiological responses such as corrected QT-interval (QTc) prolongation (Baja et al., 2010), changes in T-wave amplitude and complexity (Henneberger et al., 2005) or increased

cardiac arrhythmia (Berger et al., 2006; Peters et al., 2000) have been examined in association with air pollutants and summarized in various reviews. Moreover, a variety of studies have looked at an association between air pollutants and activation of an implanted cardioverter defibrillator. These defibrillators continuously monitor the heart rate and intervene by pacing the heart or delivering an electrical shock when abnormal rhythm is detected. Results of these studies are mixed and so far not convincing, as summed up by Anderson et al. (2010). In addition, their study, including one of the largest series of defibrillator activations did not show an association with any of the eleven monitored pollutants except for particle sulfate. In summary, Brook et al. (2010) inferred that the existing evidence is strong for cardiovascular mortality, hospitalizations and ischemic heart disease, moderate for heart failure and ischemic stroke and modest or mixed for peripheral vascular and cardiac arrhythmia/arrest. Table 4 shows studies on outcomes reflecting myocardial substrate and vulnerability.

3.3. Vascular function

There is evidence that PM-induced pulmonary inflammation can play a role in activating the vascular endothelium and that alteration in vascular tone and endothelial function are important PM-related mechanisms. Arterial vasoconstriction might be an explanation for the PM- and exercise-induced ischemia (Brook et al., 2004), as for example measured by ST-segment depression in patients with coronary heart disease (Chuang et al., 2008; Pekkanen et al., 2002).

Blood pressure

Hypertension is the single largest cause of worldwide mortality due to a chronic illness (Ezzati et al., 2002). Every 20/10 mmHg increase in arterial blood pressure (BP), even within the normotensive range, doubles the risk for cvd (Lewington et al., 2002). Still, the number of epidemiological studies on associations between ambient air pollution and BP is comparatively small and results are not consistent. Positive associations were reported by Mordukhovich et al. (2009) in repeated measurements in a sample of about 450 healthy men. An increment of 0.43 μg/m^3 of BC was associated with an increase in 1.5 mmHg in systolic and 0.9 mmHg in diastolic BP. $PM_{2.5}$ showed a positive but not statistically significant association. A recent cross-sectional study on the other hand found significant positive associations for $PM_{2.5}$ (Dvonch et al., 2009). Other studies report positive (Brook et al., 2009; Delfino et al., 2010b; Dvonch et al., 2009; Ibald-Mulli et al., 2001; Lin et al., 2009; Urch et al,. 2005; Zanobetti et al., 2004) but also null (Jansen et al., 2005; Madsen and Nafstad, 2006; Mordukhovich et al., 2009) or even negative (Harrabi et al., 2006; Ibald-Mulli, 2004) associations with different markers of air pollution (Table 5). Brook (2005) explains the differing results by differences in patient populations, potential exposure mischaracterization, diversity in the chemical composition of the measured pollutants, possible lack of confounder adjustment and suboptimal BP determination.

In general, it seems that the underlying mechanisms require a prolonged and cumulative exposure to reach the maximum effect as most studies demonstrating positive associations find a more pronounced association in relation to longer time lags, such as 5-day or even 7-day averages, rather than acute effects (Brook, 2005; Mordukhovich et al., 2009; Zanobetti et al., 2004). Although the degree of BP change is small and no risk factor for healthy people, Brook et al. (Brook et al., 2009) point out that increased BP is a plausible instigator of ischemic events in susceptible individuals as it might trigger plaque-instability. They add that increased BP

Table 4. Studies on myocardial substrate and vulnerability.

First author, year	Outcome variables	Exposure variables
	ST-segment depression	
Chuang, 2008		BC, $PM_{2.5}$
Lanki, 2008		$PM_{2.5}$ (outdoor + personal), UFP
Mills, 2007		Diluted diesel exhaust, exposure study
Gold, 2005		BC
Pekkanen, 2002		$PM_{2.5}$, UFP
	QT-interval prolongation	
Baja, 2010		$PM_{2.5}$, O_3, BC, NO_2, CO, SO_2
Henneberger, 2005		UFP, ACP, $PM_{2.5}$, OC, EC, NO_2, CO, NO
	T-wave amplitude and complexity	
Henneberger, 2005		UFP, ACP, $PM_{2.5}$, OC, EC, NO_2, CO, NO
	Arrhythmias	
Berger, 2006		UFP, ACP, $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, NO
	Implanted cardioverter defibrillator activation	
Peters, 2000		$PM_{2.5}$, PM_{10}, BC, CO, O_3, SO_2, NO_2
Anderson, 2010		$PM_{2.5}$, PM_{10}, BS, SO_4, PNC, CO, O_3, SO_2, NO_2, NO, NO_x

Table 5. Publications on air pollution and blood pressure.

First author, year	Association with air pollutants			Study description/design
	Positive	Null	Negative	
Delfino et al., 2010	BC, OC, $PM_{2.5}$ (UFP*)			Repeated measurements in 64 people with an ambulatory blood pressure monitor
Brook et al., 2009	Concentrated ambient $PM_{2.5}$			Randomized, double-blind crossover trial, 81 people in two locations
Dvonch et al., 2009	$PM_{2.5}$			Cross-sectional study
Lin et al., 2009	Indoor PM_{10} and $PM_{2.5}$			4 repeated measurements in 40 healthy students
Mordukhovich et al., 2009	BC	$PM_{2.5}$		Repeated measures in elderly men
Harrabi et al., 2006			PM_{10}	Cross-sectional study in 2612 elderly subjects
Madsen et al., 2006		NO_2, PM_{10}, $PM_{2.5}$		Population based study
Jansen et al., 2005		BC, PM_{10}, $PM_{2.5}$		Repeated measurements in 16 asthmatics/COPD patients
Urch et al., 2005	Concentrated ambient $PM_{2.5}$ and O_3			Controlled exposure in 23 healthy male volunteers
Ibald-Mulli et al., 2004			UFP, ACP, $PM_{2.5}$	Patients with cvd from three European cities
Zanobetti et al., 2004	$PM_{2.5}$			62 cardiac rehabilitation patients, repeated measurements
Ibald-Mulli et al., 2001	SO_2, TSP			2 repeated measurements in 2681 men and women

*Associations only seen during high exertion.

could in parts explain the association between $PM_{2.5}$ and strokes as well as heart failure exacerbation.

Endothelial function

The endothelium is composed of cells that not only serve as a physical barrier between blood and tissues but also act to maintain vascular homeostasis, the dynamic balance between vasodilatation and vasoconstriction. In addition, it plays an important role in the interaction of circulating cells with the vessel wall. Impaired endothelial function is associated with nearly all known cardiovascular risk factors (Ganz & Vita, 2003; Libby et al., 2002; Ross, 1999; Vita & Keaney, Jr., 2002) and is predictive of future cardiovascular events (Gokce et al., 2002; Gokce et al., 2003; Heitzer et al., 2001). Impaired function of the vascular endothelium is associated with a number of vascular changes, such as decreased vasodilatation, development of prothrombotic and proinflammatory states, and smooth muscle cell proliferation, all of which contribute to the formation and progression of chronic atherosclerotic lesions (Widlansky et al., 2003). Therefore, endothelial dysfunction as a reaction to increased ambient PM might provide further mechanistic insight into the observed associations between PM exposure and increased morbidity and mortality.

Although there are several ways to measure endothelial function, the commonly used, noninvasive method is to measure flow-mediated dilatation (FMD) of the brachial artery. Brachial artery diameter before and after an increase in shear stress induced by reactive hyperemia is assessed by high-definition ultrasound. The arterial dilatation reflects local endothelial release of nitric oxide (NO). FMD is considered a reasonable surrogate marker for assessing atherosclerosis (Perticone et al., 2001; Sorensen et al., 1997). Two pathways could lead to impaired endothelium-dependent vasodilatation: Firstly, decreased production of NO by endothelial cells and secondly, PM-induced changes in smooth muscle cells lining the vessel. To distinguish between these two pathways, some study participants receive nitroglycerin, an NO donor, as part of the vascular imaging procedure. If the vasodilatation is originally impaired by decreased NO production, this effect will disappear when external NO is given.

Several previous studies have suggested that exposure to air pollutants results in endothelial dysfunction in healthy volunteers (Briet et al., 2007; Brook et al., 2002; Dales et al., 2007; Rundell et al., 2007) (Table 6) or diseased populations (O'Neill et al., 2005; Schneider et al., 2008; Schneider et al., 2010). In addition, several studies on passive smoking reported a decrease in endothelial function after exposure to environmental tobacco smoke (Holay et al., 2004; Howard & Wagenknecht, 1999; Kato et al., 2006). Only few studies have used other methods such as pulse wave measurement (Lundback et al., 2009), measurement of changes in finger blood vessel volume with an Endo-Pat tonometer, and indirectly, by assessing the amount of NO (Gandhi et al., 2009) to examine the association between air pollutants and endothelial function with inconclusive results.

3.4. UFP and other markers of traffic-related air pollution

Most studies covered in the above-mentioned reviews examine the association between PM_{10} or $PM_{2.5}$ and

Table 6. Studies on endothelial function.

First author, year	Exposure variables	Outcome variable(s)
Gandhi et al., 2009	Diesel exhaust	Mean pulse wave amplitude (Endo PAT tonometer)
		Vascular nitrite
Lundbäck et al., 2009	Diesel exhaust	Pulse wave analysis
		Pulse wave velocity
Schneider et al., 2008	$PM_{2.5}$	Flow-mediated dilatation
		Small-artery elasticity
Briet et al., 2007	NO, NO_2, SO_2, CO, PM10, $PM_{2.5}$	Flow-mediated dilatation
		Endothelium-independent response to sublingual glycerin nitrate
		Reactive hyperemia
Dales et al., 2007	$PM_{2.5}$, UFP, NO_2	Flow-mediated dilation
Rundell et al., 2007	UFP	Flow-mediated dilatation
O'Neill et al., 2005	$PM_{2.5}$, UFP, $SO4_2$–, BC	Brachial artery reactivity (flow-mediated and nitroglycerin-mediated)
Brook et al., 2002	Concentrated ambient particles (CAP) + O3	Brachial artery diameter
		Flow-mediated dilatation
		Endothelial independent nitroglycerin mediated dilatation

cardiovascular outcomes, and evidence for UFP is still limited.

A multicentre cohort study on MI survivors showed an increased risk of cardiac readmission to hospital during days with elevated concentrations of urban air pollution, including PNC (von Klot et al., 2005). Additionally, an association was found between exposure to traffic and the onset of MI within 1 h in a study in Augsburg, Germany (Peters et al., 2004). While traveling in a car was the most common source of exposure, associations did not differ much for people who had used public transport. The overall effect estimate also did not change in multivariate analyses adjusting for stress (anger), strenuous activity or getting up in the morning—factors that are also considered to transiently increase the risk of MI. Results from the APHEA study also indicate an association between BS and hospital admission for cardiac events, especially in people over 65 years old (Le Tertre et al., 2002). Moreover, data from the UK showed a positive association between BS and cardiovascular hospital admission (Poloniecki et al., 1997).

Regarding HRV, a recent study reported an association between being in traffic in the previous 2 h and a decrease in HF (Zanobetti et al., 2010). Timonen et al. (2006) found an association between PNC and the ratio of LF to HF during a period of paced breathing up to 3 days after exposure in a panel of cardiac patients in three European cities. Park et al. (2005), on the other hand, did not see any association for HRV with PNC 4, 24 or 48 h after exposure. In a small study on 10 and 5 participants, respectively, an association between personal $PM_{2.5}$ as well as PNC measurements and HRV parameters was found (Ruckerl et al., 2009). SDNN, root mean square of successive normal-to-normal interval differences (RMSSD) and HF decreased in the 60 min after exposure to particulate air pollution with differing time-scales. Associations were more delayed but more pronounced for PNC despite the smaller number of observations.

In 2002, Pekkanen et al. (2002) reported an increased risk of exercise-induced ST-segment depression, a marker for myocardial ischemia in association with fine and ultrafine (0.01–0.1 μm in diameter) particles 2 days before the clinical visit among subjects with coronary heart disease in Helsinki, Finland. In the same database, Lanki et al. (2008) found an immediate association for $PM_{2.5}$, measured as outdoor and personal exposure, while no immediate associations for outdoor UFP could be detected. Gold et al. (2005) and Chuang et al. (2008) found similar results for exposure to BC, an indicator for particles originating from combustion processes. The observed associations provide a plausible biologic link between levels of ambient air pollution and adverse cardiac outcomes. Results of Chuang et al. also indicated that effects were greatest in patients with MI in the first month after the event.

In a panel of male patients with coronary heart disease, Henneberger et al. (2005) reported an association between UFP (0.01–0.1 μm in diameter) and T-wave amplitude and T-wave complexity, both repolarisation parameters that play a critical role in arrhythmogenesis. In the same panel, Berger et al. (2006) found an association between UFP (0.01–0.1 μm in diameter) and an increased risk for supraventricular runs and for the number of ventricular runs, reflecting an increased risk of arrhythmia from traffic-related air pollution. Zanobetti et al. (Zanobetti et al., 2009) detected an association between being in traffic in the previous 2 h and T-wave alternans, a marker of cardiac electrical instability in a panel of patients with documented coronary artery disease.

Ibald-Mulli et al. (2004) found no association between UFP (0.01-0.1 μm in diameter) and BP. More recent results from Delfino et al. (2010b) showed an association only during periods of high exertion.

3.5. Susceptible subgroups

In her review on PM and heart disease, Peters (2005) concludes that patients with pre-existing diseases such

as COPD, congestive heart disease, previous MI or diabetes might be at an increased risk of experiencing acute exacerbation of their disease on days with high concentrations of air pollution. Pope (2000) and Zareba et al. (2001) added the "elderly in general" to the list of susceptible people.

Results from the Normative Aging Study showed an association between QTc, a marker of ventricular repolarisation, and BC. In addition, the results indicate that diabetics, nonsmokers and obese participants, as well as also people with unfavorable genotypes related to oxidative stress reacted more strongly to ambient air pollution (Baja et al., 2010).

Studies on vascular function found diabetics and obese people to be especially susceptible. Associations for BP and air pollution were stronger in obese subjects in a panel of elderly patients with coronary artery disease (Delfino et al., 2010b). O'Neill et al. (2005) studied 270 residents from Greater Boston, Massachusetts. They found the strongest decrease of FMD associated with an exposure to sulfates and BC in a subgroup of 182 individuals with type 2 diabetes. Effect estimates for $PM_{2.5}$ and PNC were a little smaller and not statistically significant. Moreover, Schneider et al. (2008) found immediate changes in endothelial function in association with $PM_{2.5}$ in a panel of 22 diabetics, which was enhanced in patients with high body mass index, high glycolated hemoglobin and low adiponectin, all of them characteristics associated with insulin resistance. A study from Taiwan showed that altered cardiac autonomic function was present in people with at least one metabolic abnormality as part of a metabolic syndrome. Moreover, participants with two or more metabolic abnormalities exhibited a higher insulin resistance than subjects without metabolic abnormality (Chang et al., 2010). As obesity and impaired glucose tolerance comprise two markers of the metabolic syndrome, these results support the idea of an increased susceptibility of obese and diabetic patients.

3.6. Conclusion

Results across the different studies seem quite similar for cardiovascular hospitalization and death in association with PM_{10} and $PM_{2.5}$, indicating a conclusive association between air pollution and cardiovascular endpoints and death. For outcomes representing subclinical physiological responses results are not always in agreement, which might partly be due to different study settings and study populations.

Results for UFP are still limited and more research is needed. Recently, a Dutch research team carried out an expert elicitation, a systematic approach to generate and synthesize subjective judgments of relevant experts on a subject where well established knowledge has not been developed yet due to insufficient or contradicting data. Twelve clinical, toxicological and epidemiological experts were invited. Out of these 12 experts, 10 rated the likelihood that long-term exposure to UFP is causally related to cardiovascular morbidity as medium or high, while only two experts rated it as low (Knol et al., 2009).

4. Air pollution and blood markers of inflammation, coagulation and endothelial function

The current understanding of the biological mechanisms linking the inhalation of ambient air pollution to an exacerbation of cvd comprise very rapid effects of air pollution such as vascular dysfunction but also chronic biological effects (Brook et al., 2010). Both will be discussed in more detail in section 7 of this review. Seaton et al. (1995) hypothesized that the inhalation of particles might lead to alveolar inflammation, which increases the level of blood coagulability, thus leading to an increased risk of ischemic events in susceptible individuals. There is a strong link between inflammation and coronary heart disease because factors involved in inflammation and infections seem to play a proatherogenic role and inflammation has been identified as a risk factor for acute coronary syndrome. Systemic inflammation could result in destabilization or even rupture of vulnerable atheromatous plaques, leading to acute ischemic events.

The first study on ambient air pollution and blood markers was conducted by Peters et al. (1997a) in Augsburg, Germany. The authors compared measurements of plasma viscosity before, after and during a severe air pollution episode in 1985 in a random sample of the population. They found that plasma viscosity was higher during the air pollution episode in both men and women and after adjustment for known cardiovascular risk factors. They concluded that the increased plasma viscosity might represent a part of the pathophysiological chain linking high ambient air pollution to increased cardiovascular mortality and hospital admission. In addition, Seaton et al. (1999) examined the association of ambient PM_{10} and markers of blood inflammation and coagulation using repeated blood samples in elderly UK citizens. They found that CRP was positively associated with higher levels of PM_{10}, while hemoglobin, red blood cells and fibrinogen decreased with an increase in air pollutants. A large number of epidemiological studies on the association of ambient air pollution and various blood markers, comprising not only inflammatory blood markers but also blood markers reflecting platelet activation and endothelial function, followed the publication of these studies.

4.1. Inflammation

CRP, the classical acute-phase protein, is one of the first and most extensively studied acute-phase reactants in association with air pollution. CRP, as measured by high sensitivity (hs) assays, has appeared as a reliable and independent predictor of incident cardiovascular events (Koenig et al., 2006; Ridker et al., 1998c; Ridker et al., 1998b; Ridker et al., 1998a). Increased hs-CRP concentrations have been shown during an air pollution

episode in Germany in healthy men (Peters et al., 2001) and for ambient PM_{10} levels currently present in Europe (Seaton et al., 1999). Additionally, in a panel of coronary heart disease patients, an increase in hs-CRP above the 90th percentile was found in association with ambient particles (Ruckerl et al., 2006). A recent study using repeated measurements in an elderly panel reported a significant increase in hs-CRP levels with increased air pollutants (Delfino et al., 2008) and positive but nonsignificant associations were shown in a study in Stockholm (Panasevich et al., 2009). Hoffman et al. (2009) reported a positive association between $PM_{2.5}$ and hs-CRP from one of the few long-term studies; however, significant results were limited to men.

Some studies also show a lack of an association between various air pollutants (Hildebrandt et al., 2009) or residence close to a major road (Williams et al., 2009) and hs-CRP. A recent study in nonsmoking seniors only detected an association for hs-CRP and $PM_{2.5}$ in subjects without cvd or without intake of anti-diabetic medication (Liu et al., 2009). Hs-CRP is almost exclusively synthesized in the liver upon stimulation through interleukin-6 (IL-6), the key cytokine that stimulates the synthesis of all major acute-phase proteins (Woods et al., 2000).

Serum amyloid A (**SAA**) is also an acute-phase protein and is bound to high density lipoprotein in plasma. Although its sensitivity in evaluating an acute-phase response is almost as good as CRP, it has been studied to a much smaller extent (Thomas, 1998). Epidemiological studies on air pollution and SAA found small positive (Ruckerl et al., 2006) or no associations (Hildebrandt et al., 2009; Williams et al., 2009).

Elevated levels of **IL-6** are associated with total mortality (Harris et al., 1999) and with risk of future fatal and nonfatal MI (Ridker et al., 2000). Only a few epidemiological studies on air pollution and IL-6 have been published so far. In a study in the United Kingdom (Seaton et al., 1999), no significant associations were seen for a 3-day cumulative exposure to ambient PM_{10}. A study among 115 overweight women also found no association between IL-6 and living close to a major road (Williams et al., 2009). However, in a large European multicentre study on MI survivors IL-6 levels were significantly elevated in association with increased levels of PNC (Ruckerl et al., 2007a). A recent study in elderly subjects from the Los Angeles area also demonstrated a positive association between IL-6 and various markers of air pollution, including PNC and number concentrations of particles with a diameter < 0.25 μm (Delfino et al., 2009). However, after follow-up analyses, authors state that associations between IL-6 and number concentrations of particles with a diameter < 0.25 μm were confounded by polycyclic aromatic hydrocarbons (PAH) (Delfino et al., 2010a). Increased IL-6 levels have also been observed after exposure to high air pollution levels such as in road tunnels or during forest fires (Hilt et al., 2002; Swiston et al., 2008; van Eeden et al., 2001). In a long-term study, IL-6 was positively associated with exposure to traffic-related NO_2 emissions, whereas short-term exposure only showed positive, but nonsignificant associations (Panasevich et al., 2009).

Elevated levels of tumor necrosis factor α (**TNF α)** indicate systemic inflammation. The few studies on air pollution show positive but largely nonsignificant associations (Delfino et al., 2008; Panasevich et al., 2009). In addition, null associations have been reported (Liu et al., 2009).

Many studies have linked particulate exposure to the level of **leukocytes** (Ghio et al., 2003; Ruckerl et al., 2006; Ruckerl et al., 2007b; Schwartz, 2001; Seaton et al., 1999; Suwa et al., 2002; Tan et al., 2000; van Eeden et al., 2001); however, results are contradictory and different hypotheses regarding the underlying mechanisms have been proposed. An increase in leukocytes in association with air pollution is usually interpreted as an indication for an increased inflammatory response. A decrease in leukocytes on the other hand is more difficult to explain and the suggested explanations can only be regarded as hypotheses. The low levels in leukocytes in peripheral blood some authors report in association with an increase in particles might be a consequence of the increased levels of adhesion molecules which help circulating leukocytes to enter the subendothelial space from the blood (Luster, 1998; Rubin and Farber, 1998; von Andrian and Mackay, 2000). Increased levels of adhesion molecules in association with higher levels of air pollution have been shown previously (Jacobs et al., 2010; Ruckerl et al., 2006; Salvi et al., 1999) supporting the above hypotheses. Another possibility is that the decrease in leukocytes in peripheral blood is the result of a prolonged or delayed transit of leukocytes through the lungs following particle-induced vasoconstriction. Pietropaoli et al. (2004) showed that inhalation of carbon UFP for 2 h reduced the pulmonary diffusing capacity for CO in healthy subjects. Frampton et al. (2006) reported that similar exposures to UFP reduced the percentage of eosinophils and basophils in peripheral blood, and reduced expression of adhesion molecules on peripheral blood monocytes and granulocytes.

Seaton et al. (1999) and Ruckerl et al. (2007b) found significant decreases in **erythrocytes** and **hemoglobin** in association with PM_{10}. Seaton et al. suggested that after an alteration of adhesive properties of passing erythrocytes, they might adhere to the systemic capillaries and therefore not be measurable in peripheral blood anymore.

Publications on air pollution and inflammation are listed in Table 7a.

4.2. Coagulation

The production of **Fibrinogen**, an acute-phase reactant and coagulation factor, is stimulated by IL-6 (Gabay & Kushner, 1999). Increased concentrations of fibrinogen are considered as indicators for an imbalance in the hemostatic system and as risk factors for arterial occlusive disorders such as MI or stroke (Thomas, 1998).

Table 7a. Air pollutants and proinflammatory mediators.

First author, year	PM_{10}	$PM_{2.5}$	UFP	BS/BC	EC/OC	Other
Jacobs et al., 2010	x	x				Modeled background PM_{10} for participants' home addresses
Delfino et al., 2009		x	x	x	x	
Hildebrandt et al., 2009	x		x		x	
Hoffmann et al., 2009		x				
Liu et al., 2009		x				
Panasevich et al., 2009	x					
Williams et al., 2009						Living near major road
Delfino et al., 2008		x	x	x	x	
Swiston et al., 2008						Fire-fighters before and after a fire fight
Rückerl et al., 2007a	x	x	x			
Rückerl et al., 2007b	x	x	x			
Frampton et al., 2006			x			
Rückerl et al., 2006	x	x	x		x	
Pietropaoli et al., 2004			x			
Ghio et al., 2003						Exposure to CAPs/Filtered air
Hilt et al., 2002						Tunnel construction workers before, during and after their shift
Peters et al., 2001						Comparison of an air pollution episode with less polluted days
van Eeden et al., 2001						Exposure to forest fires
Salvi et al., 1999						Exposure to diluted diesel
Seaton et al., 1999	x					

Danesh et al. (2005) published a meta-analysis of 31 prospective studies which clearly showed a strong and independent association between elevated plasma levels of fibrinogen and various cardiovascular endpoints and total mortality.

Studies regarding its association with air pollution are inconclusive. Fibrinogen has been shown to increase in association with high levels of ambient particles such as in an air pollution episode (Peters et al., 1997a). In addition, positive associations at comparatively low levels have been shown with PM_{10} (Hildebrandt et al., 2009; Pekkanen et al., 2000; Ruckerl et al., 2007a; Schwartz, 2001), $PM_{2.5}$ (Hoffmann et al., 2009), UFP (0.01–0.1 μm in diameter), EC and OC (Hildebrandt et al., 2009) and BS (Pekkanen et al., 2000). However, null associations also (Delfino et al., 2008; Pope et al., 2004b; Ruckerl et al., 2006) and even decreases in fibrinogen concentration in association with air pollutants have been reported (Khandoga et al., 2004; Seaton et al., 1999).

Factor VII (FVII), one of the key enzymes of the extrinsic system of the coagulation cascade, is activated by **tissue factor (TF)**. Complexes of TF with factor VIIa are central to the activation of factor X and to the formation of thrombin, which mediates the conversion of fibrinogen to fibrin (Marder et al., 2004). Results for an association between air pollution and FVII in the literature are inconsistent (Hildebrandt et al., 2009; Pekkanen et al., 2000; Ruckerl et al., 2006; Seaton et al., 1999). So far, no epidemiological study has examined the association between air pollution and TF, although toxicological studies indicate an increase in TF after exposure to $PM_{2.5}$ (Sun et al., 2008)

Prothrombin fragment 1 + 2 is cleaved from prothrombin when activated to thrombin, representing a marker of activation of the coagulation pathway (Bauer et al., 1991; Rybak et al., 1981). Hildebrandt et al. (2009) observed decreases of prothrombin fragment 1 + 2 with increases of air pollution, a finding that contrasts the hypothesis of enhanced coagulability. However, elevated levels have also been reported (Ruckerl et al., 2006). For most of the coagulation factors, changing the level between 50 and 150% has little effect on thrombin generation. However, in the case of prothrombin, the rate of thrombin generation, peak activity reached and total amount of thrombin produced are proportional to the prothrombin level (Allen et al., 2004).

D-dimer is a breakdown product of cross-linked fibrin (Lowe and Rumley, 1999) and there is growing evidence that there may be an association between elevated levels of D-dimer and increased risk of future MI (Ridker et al., 1994). The few studies investigating the effects of particulate air pollutants on D-dimer show an inconsistent pattern (Hildebrandt et al., 2009) or no association (Delfino et al., 2008; Ruckerl et al., 2006).

4.3. Platelet activation

CD40 Ligand (CD40L), a trimeric transmembrane protein of the tumor necrosis family, can promote inflammatory or thrombotic response by causing platelet activation (Blumberg et al., 2003; Freedman, 2003). It has also been shown that platelet CD40L can activate vascular cells, resulting in a production of proinflammatory cytokines and cell adhesion molecules (Henn et al., 1998; Phipps, 2000). Henn et al. (1998) concluded from their study

that the generation of inflammatory signals by platelets may occur following acute mechanical damage of the endothelium, an infection of the vascular system, and also in the pathogenesis of atherosclerosis and vascular infarction. A few studies regarding the effect of air pollution particles on the CD40/CD40L pathway that have been published indicate a positive association between ambient particles and soluble CD40L/CD40 despite different study designs (Becker and Soukup, 2003; Harding et al., 2004; Ruckerl et al., 2007b).

Publications on air pollution and coagulation are listed in Table 7b.

4.4. Endothelial function

Adhesion molecules, such as **E-selectin**, **P-selectin**, soluble inter-cellular adhesion molecule 1 (**sICAM-1**) and soluble vascular cell adhesion molecule 1 (**sVCAM-1**) mediate the contact between circulating leukocytes and endothelial cells. With their help, leukocytes can leave the blood stream and enter the subendothelial space (Luster, 1998; Rubin and Farber, 1998; Thomas, 1998; von Andrian and Mackay, 2000). An increase in adhesion molecules may indicate endothelial cell activation, as an increased expression of adhesion molecules is known to reflect activation of the vascular endothelium (Hwang et al., 1997). sICAM-1 has been shown to predict acute coronary events as well as angina pectoris in a prospective cohort of apparently healthy men (Luc et al., 2003).

Positive associations between air pollutants and E-selectin have been observed (Hildebrandt et al., 2009). However, in the same study, no association between sICAM and air pollution could be detected. A similar result was reported by Delfino et al. (2008, 2009) who found that increased levels of air pollution led to higher levels of sP-selectin, but only to small and non significant increases in sICAM-1 and sVCAM-1. Calderón-Garciduenas et al. (2008c) detected significantly lower levels of sICAM-1 and s-VCAM-1 in children living in Mexico City compared to children living in a less polluted control area. They saw, however, a clear increase in inflammatory markers, such as CRP, in the children from Mexico City. Other toxicological (Bauer et al., 1991; Salvi et al., 1999) and epidemiological studies on the other hand indicate an up-regulation in sICAM-1 (Ruckerl et al., 2006) and s-VCAM-1 (O'Neill et al., 2007) expression in association with air pollutants.

Von Willebrand factor (vWF) is known as a factor of the coagulation process (Monroe and Hoffman, 2006), but in addition, may serve as a marker of endothelial dysfunction. It bridges the gap between platelets and collagen, which is exposed if endothelial cells are damaged (Marder et al., 2004). vWF reflects endothelial cell release and probably vascular reactivity. Vascular reactivity could be secondary to inflammation, and because vWF can mediate platelet adhesion to damaged endothelium, this could be a predictor of coronary events (Gardiner et al., 2004; Thomas, 1998). Plasma concentrations of vWF are elevated in patients with coronary artery disease (Whincup et al., 2002) and may predict future cardiovascular mortality (Jager et al., 1999). In healthy mice, increased vWF expression on hepatic endothelium was detected after application of carbon black UFP (Khandoga et al., 2004). An epidemiological study in COPD patients shows a clear decrease in vWF antigen with various air pollutants, including UFP (0.01–0.1 μm in diameter), EC and OC (Hildebrandt et al., 2009) while a similar designed study in patients with cvd reported positive associations for most measured pollutants (Ruckerl et al., 2006). Children from Mexico City, a highly polluted area, also showed no difference in vWF concentrations compared to control children from a cleaner city (Calderon-Garciduenas et al., 2008c).

Publications on air pollution and blood markers of endothelial function are listed in Table 7c.

4.5. Conclusion

Due to the large variety of studies, studied populations and endpoints it is very hard to draw one single conclusion for an association between blood markers and air pollutants. The general impression is that while blood markers of inflammation mostly indicate a positive association with ambient air pollution, results for adhesion markers and coagulation are still inconsistent. One has to keep in mind, though, that the coagulation process is very complex, with regulation and counter regulation playing tightly together. Therefore, measuring only one or

Table 7b. Air pollutants and markers of coagulation.

Fist author, year	PM_{10}	$PM_{2.5}$	UFP	BS/BC	EC/OC	Other
Hildebrandt et al., 2009	x		x		x	
Hoffmann et al., 2009		x				
Delfino et al., 2008		x	x	x	x	
Sun et al., 2008		x				
Rückerl et al., 2007a	x	x	x			
Rückerl et al., 2006	x	x	x		x	
Khandoga et al., 2004			x			
Pope et al., 2004		x				
Pekkanen et al., 2000	x			x		
Seaton et al., 1999	x					
Peters et al., 1997						Comparison of an air pollution episode with less polluted days

Table 7c. Studies on blood markers of endothelial function.

Fist author, year	PM_{10}	$PM_{2.5}$	UFP	BS/BC	EC/OC	Others
Hildebrandt, 2009	x		x		x	
Delfino, 2009		x	x	x	x	
Calderon-Garciduenas, 2008						Comparison of children from polluted with children from less polluted areas
Delfino, 2008		x	x	x	x	
O'Neill, 2007		x		x		
Rückerl, 2006	x	x	x		x	
Khandoga, 2004			x			
Salvi, 1999						Exposure to diluted diesel exhaust

a few selected markers at a certain time point might not lead to a clear result. Still, cautiously interpreted, even single markers can be an indicator for the biological system being off balance due to exposure to air pollution.

Most studies on blood markers and air pollution are short-term studies; however, Pope and Dockery (Pope & Dockery, 2006) concluded in their review that also long-term exposures to ambient pollutants show an association with blood markers of cardiovascular risk such as fibrinogen, platelets and white blood cell counts as well as subclinical chronic inflammatory lung injury.

Note that the field of blood markers is expanding quickly, with new and progressive assays commercially available. This review was limited to established blood markers that have been studied in more detail.

5. Air pollution and reproduction/prenatal outcomes

In 2005, the World Health Organisation (WHO) released a review of air pollution and children's health and development. They concluded that "overall, there is evidence implicating air pollution in adverse effects on pregnancy outcomes" (WHO, 2005). They also emphasized that pregnancy outcomes are an important research field, as pregnancy is an indicator of the health of the neonate/infant and low birth weight (LBW), intrauterine growth retardation (IUGR) and impaired growth in the first year can impact the health status in later life.

Sram et al. (2005) stated that fetuses are considered particularly susceptible as their developing organ system can be more vulnerable to environmental toxicants during critical time windows, because of higher rates of cell proliferation or changing metabolic capacities.

5.1. Premature births

Premature or preterm birth is defined as being born before 37 completed weeks of gestation. As such, preterm birth is not an adverse outcome in itself, but an important determinant of neonatal morbidity and mortality (Villar et al., 2004). Not many studies regarding premature births and air pollution have been published so far and the interpretation is complicated by the inconsistency of the results regarding the role of individual pollutants and the timing of exposure. However, most studies mentioned in the review of Sram et al. (2005) find a small association between markers of air pollution such as SO_2, total suspended particles (TSP) or PM_{10} and the risk of premature births. The authors therefore concluded that the evidence is still insufficient to infer causality, but that clearly more research is needed in this field. Results from more recent studies are still inconclusive. A time-series analysis on a large dataset from London, UK, found no associations between preterm births and PM_{10} at the day of birth or in the week prior to birth (Lee et al., 2008). Ritz et al. (2007), on the other hand, saw increased odds of preterm birth in a case-control study with CO and $PM_{2.5}$ in the first trimester and for CO also in the last 6 weeks before delivery. Another case-control study in California looked at exposure to $PM_{2.5}$ for the whole pregnancy period, for the first month of the pregnancy and for the last 2 weeks before delivery and detected a small positive association with $PM_{2.5}$, but the analyses did not show any difference by timing of exposure (Huynh et al., 2006). Studies in Canada (Brauer et al., 2008) and Australia (Hansen et al., 2006) observed small but significant associations with $PM_{2.5}$ and PM_{10}, respectively. While the Canadian study did not find any remarkable differences in the examined exposure windows: entire pregnancy, first and last month, first and last 3 months before delivery, the study in Australia only detected significant associations for the first 3 months and none for the last. Another Canadian study showed elevated odds of preterm birth for women whose home address was less than 200 m away from a highway (Genereux et al., 2008).

5.2. Birth weight

Fetal growth and birth weight are important indicators of the health of newborns and infants that may influence the health status in adulthood (Sinclair et al., 2007). LBW is usually defined as a term birth weight less than 2500 g (Brauer et al., 2008; Woodruff et al., 2009); however, some authors use different cut points in their analyses.

The WHO report (WHO, 2005) concluded from the reviewed studies that there is a suggested link between air pollution and LBW. However, effects differ by studies and not all results are statistically significant, especially after adjusting for potential confounders such as maternal education, maternal smoking or SES. Zeka et al. (2008) showed in a study on singleton births in Eastern Massachusetts that especially SES is associated with reduced birth weight and preterm births, and needs to be

controlled for in air pollution studies. Sram et al. (2005) infer from their reviewed studies, that evidence suggests causality of the effect of air pollution and birth weight. They point out, however, that more studies are needed to confirm the observed associations. Most studies mentioned in the WHO report (2005) examine SO_2 and TSP as exposure pollutants. Some also cover PM_{10}, CO and NO/NO_2. Other studies found small but significant reductions in birth weight in association with $PM_{2.5}$ (Bell et al., 2007; Parker et al., 2005) but also null associations have been reported for PM_{10} and NO_2 (Hansen et al., 2007).

Some recent studies use land use regression (LUR) models rather than data from central monitoring sites. LUR models take variables such as proximity to major roads, population density and land coverage into account, allowing for an individual estimate of the participants exposure at the home address. By using LUR models, Slama et al. (2007) found an increased risk of birth weight <3000 g in association with $PM_{2.5}$ levels around the maternal home address in a birth cohort of more than 1000 children in Bavaria. A study in Canada found mostly non significant associations between NO_2, NO, CO, PM_{10} and LBW for the whole pregnancy, for the first and last month of the pregnancy and for the first and last 3 months of the pregnancy (Brauer et al., 2008). In the Spanish INMA-Sabadell Cohort (Aguilera et al., 2009), LUR models were used to estimate the influence of NO_2 and aromatic hydrocarbons on birth weight. Associations between decreased birth weight and an increase in aromatic hydrocarbons were only seen for women who spent less than 2 h per day outside. No association was found for NO_2. Moreover, elevated odds of LBW were seen for women who lived within 200 m of a highway (Genereux et al., 2008). A study from Krakow measured personal exposure to $PM_{2.5}$ for 48 consecutive hours during the second trimester. They found that increased personal $PM_{2.5}$ was associated with deficits in birth weight, length at birth and head circumference at birth. Moreover, this study demonstrated a clearly higher susceptibility of male fetuses to air pollution exposure than female fetuses (Jedrychowski et al., 2009).

5.3. IUGR/small for gestational age

IUGR is defined as birth weight below the 10th percentile of the birth weight for a given gestational age and sex (WHO, 2005). The definition for "small for gestational age" (SGA) is identical to IUGR and both terms are commonly used in publications.

Authors of the WHO report (2005) concluded that there is a suggested link between air pollution and IUGR; however, studies are few and results not consistent. The four studies cited in the report mainly examined PM_{10} and $PM_{2.5}$, but also carcinogenic PAH. The majority of them suggested a positive association, especially for the first month of gestation.

More recent studies still found inconclusive evidence. A study in Vancouver, Canada, observed small but consistent associations between NO_2, NO, CO, PM_{10} and $PM_{2.5}$ and SGA despite comparatively low air pollution levels. A clear association was seen for women living <50 m from a highway (Brauer et al., 2008). Another Canadian study reported similar results for SGA in women whose residential address was within 200 m of a highway (Genereux et al., 2008). However, a study in Brisbane, Australia, did not find evidence for an increased risk in SGA in association with PM_{10} or NO_2 (Hansen et al., 2007).

5.4. Fetal growth

Data on fetal growth include various measures such as femur length, head circumference, abdominal circumference, biparietal diameter and estimated fetal weight (Aguilera et al., 2010). Only few very recent studies dealt with the association of fetal growth and air pollution. Data from the Spanish INMA-Sabadell cohort suggested a small association between biparietal diameter and aromatic hydrocarbons. When only women who spent less than 2 h per day in nonresidential outdoor locations were considered, small associations were also seen between NO_2 and growth in head circumference, abdominal circumference, biparietal diameter and estimated fetal weight at different points of the pregnancy (Aguilera et al., 2010). Hansen et al. (2007) found that an increase in NO_2 during the third trimester was associated with a reduction in crown-heel length; however, none of the other outcomes or exposures showed an association.

5.5. Birth defects

Up to now, only five studies have examined the association between air pollution and birth defects. Birth defects mostly concern cleft lip with or without cleft palate and various forms of congenital heart defects. The first one, conducted in Southern California, found an increased risk for congenital heart defects such as ventricular septal defects, aortic artery and valve defects or pulmonary artery and valve anomalies with CO and ozone, while results for NO_2 and PM_{10} were inconclusive (Ritz et al., 2002). A case-control study in Texas reported positive associations between CO, PM_{10} and SO_2 and some heart defects (Gilboa et al., 2005). Hwang and Jaakkola (2008) found evidence for an adverse effect of ozone on the risk of cleft lip with and without cleft palate in a large Taiwanese case-control study. No associations were seen for SO_2, NO_x, CO or PM_{10}. In a cohort from Atlanta, Georgia, a statistically significant association was observed for PM_{10} and patent ductus arteriosus, while none of the other examined pollutants or outcomes showed any association (Strickland et al., 2009). Hansen et al. (2009) used a case-control design to examine associations between air pollution and births between 1998 and 2004 in Brisbane, Australia. Data only showed associations when the analyses were restricted to mothers who resided within 6 km of an ambient air quality monitor. Moreover, they saw associations between SO_2 and ozone with cleft lip with or without cleft palate and congenital heart defects. However, inverse associations were also found and a reliable conclusion could not be drawn.

Summing up, the associations between air pollution and birth defects are small and vary between the different studies. A general problem of most of the cited studies is the large number of statistical tests that was carried out, which only revealed few statistically significant associations. It is very hard to judge whether these associations are real or just chance findings.

5.6. Infant mortality

Infant mortality, the number of deaths in the first year of life, is usually divided into neonatal mortality (death within 0–27 days of life) and postneonatal mortality (death between 28 days and 1 year of life) (Glinianaia et al., 2004).

The first ecological studies which connected air pollution to children's health date back as far as the early 1970s, using data from 1958 to 1964 (Collins et al., 1971) or 1950 (Sprague and Hagstrom, 1969). Starting from the 1990s, a large number of ecological, cross-sectional and time-series studies followed (WHO, 2005). The WHO report in 2005 concluded that there is solid evidence of an association between air pollution and infant mortality, primarily due to respiratory deaths in the post neonatal period. They also infer from the reviewed studies that the effect is mainly due to particulate air pollution (WHO, 2005). Sram et al. (2005) come to the same conclusion, highlighting the remarkable consistency of the results of different study designs and areas. They point out that maternal smoking could be the only alternative explanation for these findings. However, time-series analyses, which by design control for personal parameters such as smoking, reveal the same effects as other study designs, which makes maternal smoking unlikely as an explanation (Sram et al., 2005). Glinianaia et al. (2004), on the other hand, who conducted a systematic review on the association between air pollution and infant death, concluded that in general the association between particulate air pollution and infant mortality was inconsistent and differed between different subgroups of infant mortality. Estimates were more concise for postneonatal mortality due to respiratory causes and sudden infant death syndrome.

More recent studies which were conducted after the release of the WHO report and the reviews mentioned above mainly confirm an association between air pollution and postneonatal mortality (Ritz et al., 2006; Woodruff et al., 2006; Woodruff et al., 2008). However, analyses of data over 10 years in 10 major cities in the UK only showed a small increase in infant mortality with SO_2 and no associations with any of the other pollutants such as PM_{10}, CO, O_3 or NO_2 (Hajat et al., 2007). A study using traffic density rather than single pollutants found a positive association between traffic exposure and early neonatal mortality for women living in the highest quartile of traffic density (de Medeiros et al., 2009).

5.7. Sperm quality

Only a few epidemiological studies deal with different aspects of sperm quality in association with air pollution. First studies in the mid-nineties examined semen quality in association with air pollution in the Czech Republic (Sram et al., 1996). Young men were found to be at greater risk of having abnormalities in sperm morphology and chromatin integrity after exposure to periods of elevated air pollution (Selevan et al., 2000; Sram et al., 1996). Sperm chromatin is essential for sperm function and subsequent embryonic development and defects in sperm chromatin are linked to natural reproductive malfunctions, like spontaneous abortion (Wu & Chu, 2008). A follow-up study using repeated measurements in a subset of these study participants showed associations between total episodic air pollution and abnormalities in sperm chromatin (Rubes et al., 2005). No association was found between air pollution and total sperm count. More recent studies reported associations between ozone and average sperm concentration in a repeated measurement study in Los Angeles, California. However, none of the other measured pollutants such as NO_2, CO or PM_{10} were significantly associated with sperm quality outcomes (Sokol et al., 2006). A small study indicated a lower sperm count and decreased semen motility as well as a worse ratio of sperm cells with normal morphology in men working as toll collectors who experience diesel exposure on a regular basis, in comparison to men working as office personnel (Guven et al., 2008). Moreover, Hammoud et al. (2009) reported negative correlations between exposure to $PM_{2.5}$ and sperm motility 2 and 3 months after exposure. Hansen et al. (2010), on the other hand, found no or only weak associations between air pollutants and sperm quality.

5.8. UFP and other markers of air pollution

No studies examining the association between any of the birth outcomes and UFP have been published so far. The authors of the INMA-Sabadell study (Aguilera et al., 2009) annotate that exposure assessment can be improved by using geographic information systems (GIS) and LUR models which take small-area variations in vehicle exhaust pollutants into account. These more advanced techniques have only been used in studies on birth weight so far, but not with any other outcome.

5.9. Conclusion

Birth outcomes and air pollution is still a comparatively young research field and an important point to justify more research is to answer the still open question of whether early exposure and impaired reproductive outcome have long-term consequences in later life (Sram et al., 2005). Apart from this, many unresolved questions and problems remain.

One big challenge is to identify the most vulnerable periods of exposure for adverse outcomes. The fetus might have varying susceptibility in different periods of the pregnancy which also makes comparison of and conclusions from studies difficult. Also confounding, especially from SES, is a problem in the analyses. Social class indicators are thought to be important confounders as

women with lower SES are at increased risk of poor birth outcomes and, at least in some countries, are more likely to live in polluted areas (Woodruff et al., 2009). Généreux et al. (2008), however, found that proximity to a highway led to adverse birth outcomes especially in mothers from high SES neighborhoods and with a high educational level, a finding that is counterintuitive. Zeka et al. (2008), on the other hand, showed in a study on singleton births in Eastern Massachusetts that especially SES is associated with reduced birth weight and preterm births, and needs to be controlled for in air pollution studies. For pregnancy outcomes, consideration of women's residential mobility and time-activity patterns during pregnancy also requires consideration (Aguilera et al., 2009). Moreover, the contribution of different PM compounds, especially UFP, needs to be examined and biological pathways require further clarification. One important advantage, however, is the defined and relatively short time span of exposure during pregnancy (Woodruff et al., 2009).

6. Air pollution and neurotoxic effects

While adverse associations between air pollutants and the cardiovascular system have been shown in a large number of publications, it has only recently been discovered that these deleterious effects may extend to the brain (Peters et al., 2006; Veronesi et al., 2005) and research in this area is still limited.

6.1. Air pollution and stroke

One of the first studies that detected an impact of air pollution on the brain was a study from Shanghai, which found an increase in stroke in people exposed to indoor coal fumes (Zhang et al., 1988). A small association between stroke mortality and UFP was seen in Helsinki, a city with very low air pollution levels. The association was limited to the warm season and was clearer when the analyses were restricted to ischemic stroke mortality (Kettunen et al., 2007). Associations between air pollutants and stroke, especially ischemic stroke, have been confirmed in further studies (Chen, 2010; Henrotin et al., 2007; Hong et al., 2002b; Hong et al., 2002a; Kan et al., 2003; Kettunen et al., 2007; Miller et al., 2007; Oudin et al., 2010; Tsai et al., 2003; Vidale et al., 2010; Wellenius et al., 2005). However, a Canadian study only found an association between ischemic stroke and $PM_{2.5}$ in patients with diabetes mellitus (O'Donnell M et al., 2009) and there was no association between stroke mortality and air pollution in the ACS study (Pope et al., 2004a).

6.2. Air pollution and diseases of the central nervous system

The first evidence for an association between air pollution and neurodegenerative diseases came from studies in feral dogs in Mexico. Feral dogs living in highly polluted areas showed enhanced oxidative damage and premature presence of diffuse amyloid plaques, insoluble fibrous protein aggregates that may play a role in various neurodegenerative diseases. Moreover, the authors found a significant increase in DNA damage in olfactory bulbs, frontal cortex and hippocamus compared to dogs from lower polluted areas (Calderon-Garciduenas et al., 2002; Calderon-Garciduenas et al., 2003). Both chronic respiratory tract inflammation and breakdown of the nasal respiratory and olfactory barriers may contribute to brain inflammation by increasing the access of air pollutants to the brain (Calderon-Garciduenas et al., 2003; Feron et al., 2001). These findings were recently confirmed in further animal studies and also in humans (Calderon-Garciduenas et al., 2008a; Calderon-Garciduenas et al., 2008b). Inflammatory processes in the central nervous system (CNS) are crucial in neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD), the two most prevalent neurodegenerative diseases (Hirtz et al., 2007).

In addition, changes in cognitive function have been shown to be associated with PM. A prospective birth cohort among children in Boston, MA, showed that long-term concentration of BC, the major component of traffic-related particles, was associated with decreases in cognitive test scores in children about 9 years of age even after adjustment for confounders such as SES, tobacco smoke exposure and birth weight (Suglia et al., 2008). A birth cohort in Spain examined the association between home outdoor NO_2 levels as a proxy of individual exposure to traffic-related air pollution and cognitive development at the age of 4 years. Results show a negative, however not statistically significant, association between NO_2 and cognitive function. These results indicate that traffic-related air pollution may have a negative effect on infant cognitive function, even at comparatively low exposure levels (Freire et al., 2010). A study on elderly women in Germany insinuates that chronic exposure to traffic-related air pollution may be involved in the development of mild cognitive impairment, which is a transitional state between normal ageing and neurodegenerative diseases such as AD. The exposure was estimated by proximity of the residential address to a busy street. The effect of living near a street with heavy traffic was equally pronounced in urban and rural environments. However, authors could not exclude that the association, or parts of it, were actually caused by the noise that is associated with living close to a major road, rather than air pollution (Ranft et al., 2009). In an exposure study, electroencephalograms of 10 human volunteers showed an increase in the median power frequency in response to diesel exhaust but not filtered air in the frontal cortex. These findings suggested a functional effect on the human brain in response to diesel exhaust, indicating a general cortical stress response (Cruts et al., 2008).

The association between exposure to PM and neurological effects was further supported by a study on smokers, which showed a dose-dependent increase in the risk of developing AD disease in later life (Tyas et al., 2003). In addition, a large population based study in English nonsmokers found that high exposure to environmental

tobacco smoke, as determined by cotinine saliva levels, was associated with higher odds for cognitive impairment (Llewellyn et al., 2009).

Possible pathways linking air pollution to neurodegenerative diseases are discussed in section 7 of this review.

7. Pathways/potential mechanisms explaining the association between air pollution and adverse health effects

The previous sections summarized a large number of observed adverse health effects associated with air pollution in humans. Figure 2 gives an overview on what organs might be affected by air pollution. Potential pathways and conceivable mechanisms of how particles of different size classes and chemical composition can affect health will be discussed in this section.

7.1. Pulmonary effects

It has been shown that particles have the potential to cause oxidative stress in the lungs, which is an important part of their pathogenic mechanism (Brook et al., 2003). Oxidative stress can lead to inflammation and as a consequence to fever, fibrosis, bronchitis etc. Moreover, it can entail oxidative adducts in the epithelium that have the capacity to contribute to carcinogenesis (Donaldson et al., 2005; Kunzli and Tager, 2005). Schwartz (Schwartz, 2004) pointed out a number of studies which showed that increased exhaled NO was associated with several air pollutants in individuals without, but particularly with diagnosis of asthma. There is also evidence that pollution plays a role in increased lung inflammation, especially in patients with asthma.

7.2. Cardiovascular effects

As shown in Sections 1 and 3, air pollution can have chronic (long-term) as well as acute (short-term) effects on the cardiovascular system and potential mechanisms might differ. A number of newer studies have demonstrated very rapid effects of air pollution on health outcomes such as vascular dysfunction, which supports the idea that at least some pathways convey signals systemically within hours after exposure.

There are, on the other hand, also studies that suggest chronic biological effects, such as the promotion of atherosclerosis. Particle-induced progression of atherosclerosis is one of the main hypothesized pathways for chronic effects (Brook et al., 2010). Mills et al. (2009) inferred from clinical and toxicological studies that not only the atherosclerotic burden increases by PM exposure, but also that the resultant lesions might be more vulnerable to plaque rupture events (Mills et al., 2009). They base their conclusion on studies of apolipoproein-E-knockout mice fed with a high fat diet which showed increases in aortic plaque area and burden when exposed to $PM_{2.5}$ compared to filtered air (Sun et al., 2005). In addition, data from hyperlipidemic rabbit models showed more advanced coronary and aortic atherosclerotic plaques than control rabbits after instillation of ambient PM_{10} (Suwa et al., 2002). A more recent study in apolipoprotein E-deficient mice showed that exposure to UFP (particle diameter <0.18 μm) lead to larger early atherosclerotic lesions in the animals than exposure to $PM_{2.5}$ or filtered air (Araujo et al., 2008). Moreover, a large epidemiological study from Los Angeles, USA, reported that carotid intima-media thickness, a measure of subclinical atherosclerosis, increased with higher $PM_{2.5}$ levels at the participants' homes (Kunzli et al., 2005). A German study showed positive associations between the probability of having high coronary artery calcification scores and proximity to a major road in more than 4000 participants (Hoffmann et al., 2007).

A number of mechanisms have been proposed to explain the adverse health effect of PM. Supportive evidence has been found for inflammation, cytokine and chemokine release, production of white blood cells,

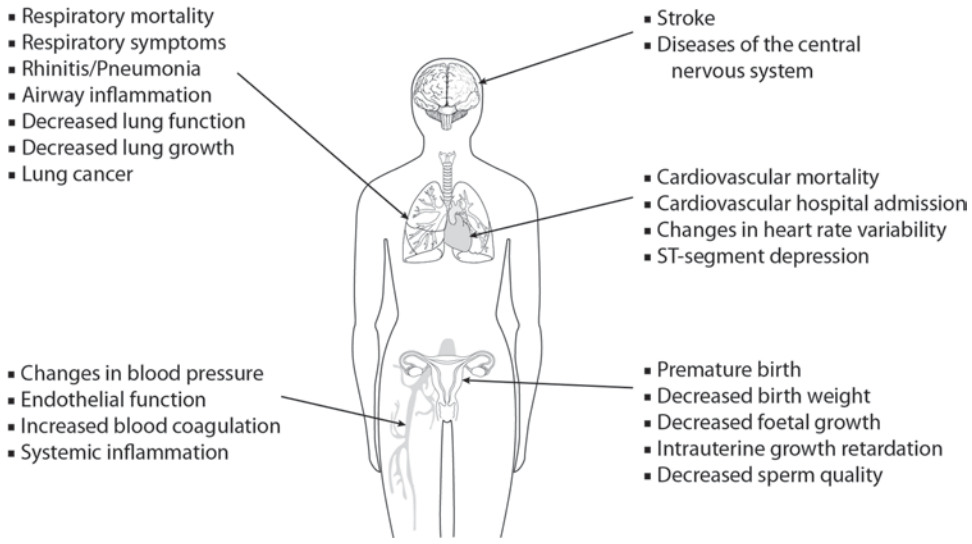

Figure 2. Organs of the human body that can be affected by air pollution (from Peters et al., J Occup Environ Med. 2011 Jun;53(6 Suppl):S8-S13).

production of free radicals in the lungs and stimulation of irritant receptors (Nel et al., 1998). At the molecular level, evidence supports an important role of pathways that work via reactive oxygen species (ROS) resulting in pulmonary oxidative stress, systemic inflammatory responses, vascular dysfunction, stimulation of capsaicin receptors or atherosclerosis (Araujo & Nel, 2009; Brook et al., 2010).

As opposed to chronic risk factors which determine a vulnerability to acute coronary events, acute effects are mediated by transient risk factors that might trigger acute events in susceptible populations (Peters et al., 2004). The major cause of coronary syndrome and cardiovascular death is a disruption of an atherosclerotic plaque and thrombus formation. The association between ambient air pollution and acute cardiovascular events could therefore be due to alterations in thrombus formation or behavior of the vessel wall (Mills et al., 2009). Another possible contributor to the incidence of sudden cardiac death is an autonomic imbalance which may lead to the triggering of cardiac arrhythmias (Singer, 1995).

Hypothesized pathways

Today, three main pathways linking ambient air pollution to cardiovascular health are being discussed (Figure 3); however, the complex combination and interaction of mechanisms are still not fully understood (Brook et al., 2010; Brook et al., 2004; Knol et al., 2009; Mills et al., 2009; Pope and Dockery, 2006; Schulz et al., 2005). None of the suggested pathways might work exclusively and the extent to which these pathways overlap is unknown.

1) Particles deposited in the pulmonary tree can alter systematic autonomic balance leading to parasympathetic nervous system withdrawal and/or sympathetic nervous system activation. These effects can be either triggered directly, by stimulating pulmonary neural reflexes or indirectly, by provoking oxidative stress and inflammation in the lung, or a combination of both. Alterations in autonomic tone can contribute to the instability of a vascular plaque or initiate cardiac arrhythmias.

2) Circulating pro-oxidative and/or proinflammatory mediators released from the lungs may induce a systemic chain reaction. Such mediators include cytokines (e.g., IL-6), acute-phase reactants (e.g., CRP and fibrinogen), vasoactive hormones (e.g., endothelins) and activated leucocytes, which may lead to endothelial dysfunction and a pro-coagulatory state with thrombus formation and promotion of atherosclerotic lesions (Brook, 2008; Brook et al., 2004; Donaldson et al., 2005; Schulz et al., 2005). Persistently elevated concentrations as well as acute changes in concentrations of inflammatory markers have been associated with an increased risk of cardiovascular events in large cohort studies (Koenig et al., 1999; Ridker et al., 1997).

3) After inhalation, UFP or soluble particle constituents may rapidly translocate from the pulmonary epithelium into the circulation and interact directly with the cardiovascular system (Geiser, 2002). These small particles might not only affect the vascular endothelium and atherosclerotic plaques but also provoke local inflammation and oxidative stress. Several studies on animals (Nemmar et al., 2001; Nemmar et al., 2004; Oberdorster

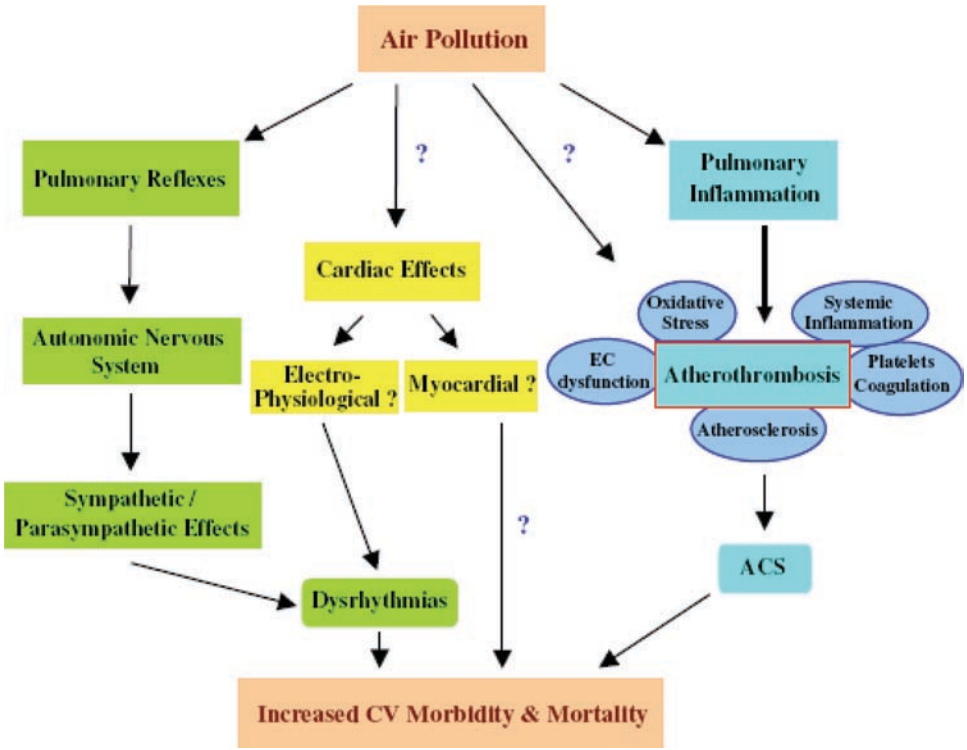

Figure 3. Possible pathways linking air pollution and cardiovascular morbidity and mortality. From (Araujo and Nel 2009).

et al., 2002; Semmler et al., 2004) and humans (Mills et al., 2006; Nemmar et al., 2002) demonstrated extrapulmonary translocation of UFP.

Once in the circulation, UFP might also have direct effects on the heart and other organs. Direct pollutant effects are hypothesized to trigger acute cardiovascular events occurring within a few hours after exposure (Brook, 2008; Brook et al., 2004; Donaldson et al., 2005; Schulz et al., 2005). Indirect air pollutant effects caused by systemic oxidative stress and inflammation, on the other hand, are supposed to evoke rather delayed and chronic cardiovascular responses.

Pathway 1 may be partially, whereas pathway 3 may be entirely, initiated without requiring the generation of lung inflammation (Brook, 2008). While translocation of particles into the blood stream (pathway 3) is limited to UFP, the other two pathways may well be possible for coarser PM fractions (Knol et al., 2009).

7.3. Prenatal outcomes

The biological pathways that connect air pollution exposure during pregnancy to adverse prenatal outcomes are not quite clear yet. Possible biological mechanisms are nicely summarized in the meeting report by Slama et al. (2008). In short, they give three hypotheses. Firstly, pollution induced increases in plasma viscosity (see section 4 of this review) and artery vasoconstriction may influence maternal-placental blood exchange and this way impact fetal growth. Secondly, endocrine disruption caused by an interfered steroidgenesis and/or progesteron production might be involved in causing intrauterine growth restriction. Air pollutants such as heavy metals or diesel exhaust are hypothesized to lead to an endocrine disruption. Thirdly, particle-induced oxidative stress and inflammatory processes may lead to preterm births. Work by Engel et al. (2005) showed that common genetic variants in proinflammatory cytokine genes were associated with spontaneous preterm birth. Moreover, inflammatory processes might modulate host defense mechanisms and alter maternal immunity, thus leading to increased susceptibility to infections, which may then lead to intrauterine growth restriction or preterm labor. Increased oxidative stress also seems to be negatively associated with sperm motility and concentration (Agarwal et al., 2008; Desai et al., 2010).

7.4. Neurotoxic effects

Different pathways have been hypothesized to explain neurotoxic effects of air pollution, especially of PM. The main hypotheses comprise air pollution-induced inflammation and/or oxidative stress and a translocation of UFP to the brain.

Systemic inflammation might lead to cellular damage and modification of the ROS/cytokine milieu in the brain, and may also alter the cellular make-up of innate immune cells in the brain. In addition to neuronal damage, systemic inflammation caused by air pollution may contribute to deteriorating olfactory, respiratory and blood-brain barriers to enhance access to the CNS and further increase in neuropathology (Block and Calderon-Garciduenas, 2009). Toxicological studies in rodents have demonstrated that ambient particles present in urban air pollution enhance neuroinflammatory markers in the brain of mouse models (Campbell et al., 2005; CampBell et al., 2009; Kleinman et al., 2008; Veronesi et al., 2005). Prolonged exposure to diesel exhaust was also shown to induce a neuroinflammatory response in the rat brain (Gerlofs-Nijland et al., 2010). Moreover, oxidative stress may increase the susceptibility for neurodegenerative diseases (Peters et al., 2006).

In a critical update following a workshop on potential neurotoxic effects of UFP, Peters et al. (2006) summarized the evidence for the mechanisms involved in the translocation of particles from the lung to other organs, including the brain. *In vitro* studies showed that in particular UFP translocate quickly from the lungs into the cells and especially the blood. UFP can penetrate lung tissue compartments and this way reach capillaries and circulating cells (Block & Calderon-Garciduenas, 2009). Animal models have shown that inhaled or nasally instilled particles translocate into the brain in rodents (Oberdorster et al., 2004) and very recently PM was also identified in the human brain (Calderon-Garciduenas et al., 2008b).

The mechanisms responsible for PM entry into the brain are still under discussion. Possible pathways are active transport, a leaky blood-brain barrier and translocation along the olfactory bulb (Block & Calderon-Garciduenas, 2009). The olfactory pathway offers direct access to the olfactory bulb, and olfactory neurons loaded with PM have already been seen in children (Calderon-Garciduenas et al., 2008b).

7.5. Particle properties

Although consistent associations between ambient air pollution and adverse health effects have been shown, unexplained geographical and seasonal differences exist. One explanation might be that such differences are caused by variations in the chemical composition (Bell et al., 2009). PM is composed of solid and liquid particles that come from various sources, for example vehicle exhaust, road dust, forest fires or wind blown soil. Combustion particles consist of an EC core surrounded by a layer of chemicals such as organic hydrocarbons, metals, nitrates and sulfates. The carbon core as well as the enclosing chemicals determine the toxicity of the particle (Donaldson & Tran, 2002; Nel, 2005). Depending on size, surface area and chemical composition particles might pose different health risks, due to different characteristics of the particle, but also due to differing deposition patterns in the respiratory tract. The respiratory tract can be divided roughly into three regions: the nasopharyngeal, the tracheobronchial and the alveolar region (Araujo and Nel, 2009). Larger particles deposit mainly in the nasopharyngeal

and tracheobronchial region, while particles of about 20 nm, which correspond to the particle peak size of ambient urban aerosols deposit preferably in the alveolar region, and only about 15% of this particle size deposit in the tracheobronchial and nasopharyngeal region (Araujo & Nel, 2009; Oberdorster et al., 2005).

Donaldson et al. (2005) show in their review that components of combustion derived particles can cause oxidative stress through different characteristics. Diesel exhaust, for example, acts through its composition of organics, transition metals and surface area while the inflammatory properties of carbon black and coal fly ash are determined mainly through their surface area.

Meanwhile, it has been established that organic and metal PM components such as copper, vanadium, chromium, nickel and iron can induce proinflammtory effects in the lung due to their ability to cause oxidative stress (Li et al., 2003; Nel, 2005; Nel et al., 1998; Saldiva et al., 2002). Bell et al. (2009) found that nickel and vanadium content in particles explained 37% of the heterogeneity in cardiovascular hospital admission due to $PM_{2.5}$ for 106 US counties. Quinones present in PM can act as catalysts to produce ROS directly and may be key compounds in PM-based oxidative stress. In addition, particle bound transition metals or organic compounds might catalyze Fenton reactions, leading to local oxygen radical production in the lung after inhalation.

Pro-oxidative organic hydrocarbons, like PAH, on the other hand, can induce oxidative stress indirectly through biotransformation by enzymes such as cytochrome P450 (Li et al., 2003).

In addition, airway epithelial cells and macrophages produce ROS as a reaction to particle uptake by biologically catalysed redox reactions in the cell membrane and mitochondria (Jones et al., 1990; Li et al., 2003; Nel, 2005; Nel et al., 1998). ROS can damage cellular proteins, lipids, membranes and DNA (Nel, 2005). Araujo and Nel (2009) hypothesized that PM ability to induce ROS generation might be the key in promoting atherosclerosis, which could be the result of PM-mediated systemic prooxidant and proinflammatory effects.

UFP

UFP have the largest surface area and the highest content of potentially harmful hydrocarbons (Nel et al., 1998). Due to their small size, high number concentration and relatively large surface area per unit mass UFP have unique characteristics, including increased adsorption of organic molecules and enhanced ability to penetrate cellular targets in lung and systemic circulation (Li et al., 2003; Utell and Frampton, 2000). Traditionally, PM is measured as mass per space, however, particles below 100 nm contribute little to the overall mass, but represent more than 85% of the total $PM_{2.5}$ particle number. It is hypothesized that these larger particle numbers might lead to larger biological effects (Araujo and Nel, 2009). In addition, UFP contain large amounts of organic carbon and pro-oxidative PAH, which can promote oxidative stress. The high number concentration along with a large surface-to mass ratio could result in a large bio-available surface, which leads to a greater bio-availability of the bio-reactive chemicals on the particle surface. As described before, smaller particles show a different deposition pattern than larger particles, i.e. they penetrate deeper into the lungs. Better airway deposition might translate into better retention, cellular uptake and greater propensity to induce systemic effects (Araujo & Nel, 2009). Table 8 shows a comparison of the characteristics of different PM fractions.

Li et al. (2003) demonstrated that UFP collected in the Los Angeles basin were more potent than fine and coarse particles from the same area, regarding their potential to induce oxidative stress. Using electron microscopy, they also showed subcellular penetration and mitochondrial damage by UFPs, and to a lesser extent, fine particles.

After inhalation, inhaled fine particles and UFP appear to follow different routes in the organism (Kreyling et al., 2006). Unlike larger fine particles, UFP seem to escape phagocytosis by alveolar macrophages and are translocated to extrapulmonary organs (Oberdorster and Utell, 2002), leading to the production of oxygen radicals (Nemmar et al., 2002; Nemmar et al., 2004; Oberdorster et al., 2004; Oberdorster and Utell, 2002) due to their surface area properties (Dick, 2003) through redox-sensitive pathways such as mitogen-activated protein kinase (MAPK) and transkription factor NF-κb (Donaldson et al., 2005). The MAPK pathways transduce signals that lead to diverse cellular responses such as cell growth, differentiation, apoptosis and stress responses to environmental stimuli (Silbajoris et al., 2000).

Although the accumulated doses to secondary target organs are two to three times of magnitude less when compared to the lung dose, the estimated particle numbers are indeed not negligible. Considering the insoluble fraction of ambient ultrafine carbonaceous particles being inhaled continuously by each individual, one can assume that not only the EC load in the lungs increases with age but also the EC loads in the secondary target organs (Kreyling, 2006).

Table 8. Characteristics of different PM fractions, adapted from Araujo 2009.

Parameter	Fine particles ($PM_{2.5}$)	Ultrafine particles
Number per μm^3	xx	xxx
Mass per μm^3	xx	x
Surface area	xx	xxx
Lung penetrability	xx	xxx
Relative content (% of total mass)		
EC	xx	xxx
OC	xx	xxx
PAH	x	xxx
Metals	xx	x
Redox activity	xx	xxx

7.6. Conclusion

Different hypothesis on how air pollution can potentially affect the body have been described, which usually cover the lungs but also the cardiovascular system and other organs such as the brain. Although epidemiological studies by nature can never prove hypothesized pathways, the large number of studies forms a sound basis for evidence. With the support of toxicological studies, the potential mechanisms described in this section are now widely accepted. While for the lung the pathway via oxidative stress/inflammation is straightforward, there are three hypothesized mechanisms for the cardiovascular system, which might be overlapping and even aggravate each other.

These hypotheses also indicate that UFP, due to their ability of migrating from the lungs into the bloodstream and therefore in any possible organ, might be more harmful than larger particles. Moreover, they have a higher oxidative potential due to their large surface area. Despite the large body of evidence, more studies, especially on UFP are needed.

8. Research potential and outlook

The previous sections showed how air pollution can affect human health and that some population groups are more affected than others. However, knowledge with regard to different outcomes and exposures is not evenly distributed. While, for example, a large body of evidence exists for an association between air pollution and cardiovascular and pulmonary diseases, only little is know about neurotoxic effects. Regarding exposure, evidence was compelling enough for politicians to legislate daily and yearly average limits for PM_{10} and $PM_{2.5}$; however, not enough data on UFP has been collected yet to lead to similar regulations. The following section tries to assess additional research needs to fill these gaps of knowledge.

8.1. Research needs-outcomes

The amount of research conducted on specific outcomes is discussed in the first six sections of this review. It shows clearly that a lot of publications exist in some of the fields, whereas in others, there are still white spots to be filled. Please note that these tables do not state anything about the direction of the associations.

A lot of research has been conducted on mortality, especially for PM_{10} and $PM_{2.5}$. There are more short-term studies than long-term studies, but in general the amount of collected data and publications is quite large. The focus is on PM_{10} and $PM_{2.5}$ and little is know about certain pollutants such as UFP, BS/BC or EC/OC. In particular, to this date, there seems to be only one long-term study examining the association between BS and mortality (Hoek et al., 2002), while UFP, and EC/OC have not been investigated in association with mortality. This is a major disadvantage as estimates between long-term exposure and mortality have influenced in particular air quality standard setting.

There is also a quite large number of studies on pulmonary effects. They focus mainly on long-term studies on lung function, lung function growth and acute respiratory symptoms. Most short-term studies also examine lung function and acute respiratory symptoms. As with mortality studies, the commonly used exposure variables are PM_{10} and $PM_{2.5}$. There are a few short-term studies on UFP, but none for long-term; BS/BC as well as EC/OC are also clearly underrepresented.

Regarding cardiovascular effects, the number of short-term studies on hospital admission due to cardiovascular effects is much larger than the number of long-term effect studies. As with the other outcomes, studies are very much centered on PM_{10} and $PM_{2.5}$. Studies on ECG-related endpoints are by design only short-term studies. In addition to studies looking on ECG-related endpoints, a growing number of markers of vascular function have been examined. Other than for hospital admission, there are at least some studies which examined an association with UFP, BS/BC and/or EC/OC.

This review shows that quite a bit of research has been conducted on air pollution and blood markers reflecting inflammation, coagulation and endothelial function. Studies on blood markers comprise mainly short-term but also some long-term studies. In the past years, the use of LUR models, which will be described in more detail below (section 8.2), has facilitated the conduction of long-term studies on blood markers. One has to keep in mind that there is an enormous number of blood markers that can possibly be examined, reflecting different pathophysiological pathways. Moreover, most studies report more than one blood marker in association with air pollution. Detailed information on which blood markers and air pollution measures were reported can be found in the previous sections.

The youngest research fields with the smallest number of publications examine associations between air pollution and reproduction as well as neurotoxic effects. For both, evidence is still limited and also restricted to few exposure markers.

Summing up, from the outcomes' perspective, clearly more research is needed on neurotoxic effects and reproduction. Moreover, for all health outcomes, studies on UFP, BS/BC and EC/OC are rare or missing. Regarding mortality, long-term studies on UFP, BS/BC and EC/OC are needed. Long-term studies are expensive and, by design, take years before results can be published. However, long-term air pollution studies are needed as they have played an important part in recent health impact assessments and in the discussion about new air quality guidelines for Europe (Kunzli et al., 2000). Mauderly et al. (2010) also point out that although the list of examined health effects is long: "it seems doubtful that we have yet identified the full scope of outcomes having statistical relationships to measures of air pollution and it is certain that we have not discovered all of the subclinical and physiological responses that might be associated with air pollution". Moreover, with genetic examinations

becoming more common, more studies show that an unfavorable genetic predisposition may be an additional susceptibility factor for air pollution effects. In addition to the "traditional" susceptible subgroups that have been mentioned in the previous sections, people that are thought to be susceptible toward environmental stressors due to their genetic background currently gain importance.

Moreover, the past years have seen an explosion of interest in the epigenetics of cancer as a consequence of realizing that DNA methylation changes are involved in human malignancies. Therefore, it is still quite novel and timely to assess changes in DNA methylation in association with environmental stressors. Methylation can be seen as a genome defense system, and DNA methylation plays a key role in the gene-expression regulation.

8.2. Research needs-exposure

This review shows a clear imbalance when it comes to the reported air pollution exposures. For most outcomes there are a number or even a lot of studies on PM_{10} and/or $PM_{2.5}$, while studies on UFP, BS/BC and EC/OC are still rare, although it has become clear that the spatial and temporal variation of UFP cannot be captured by measuring particle mass (Pekkanen and Kulmala, 2004). Only for blood markers of inflammation, coagulation and vascular function there are several studies using UFP, BS/BC and EC/OC, while for all other research outcomes described in this review, the number of studies is insufficient. Due to this missing information, a European expert panel elicitation was used to estimate concentration-response functions for UFP (Hoek et al., 2010). The panel consisted of four epidemiologists and toxicologists, respectively, and three clinicians, all of whom were familiar and had published in the field of health effects of UFP. The estimated percentage decrease in all-cause mortality for a decrease in UFP of 1000 particles/cm^3 ranged between 0.1 and 1.2%, the median was 0.30%. The lack of long-term studies on health effects of UFP was considered the most important factor accounting for a large amount of uncertainty in the estimation (Hoek et al., 2010).

The fact that in most studies merely the number of particles per m^3 for UFP is used as exposure variable represents another gap of knowledge. The chemical composition or whether the particles are liquid or solid, and if solid, soluble or insoluble might lead to different health effects and might explain the inconsistencies that have been observed in the association of PNC with indices of health. The reported health effects might also be more a measure of freshly formed particle surfaces rather than size. However, these issues have not been adequately addressed yet.

8.3. Outlook

Besides the gaps in knowledge described in the previous paragraphs, advances in methods and knowledge need to be taken into account. Points to be addressed are a better estimation of personal exposures and pollutant mixtures. Moreover, identifying the culprit components within the PM mixtures is a challenge that still needs to be overcome. One step in the right direction may be the use of multipollutant models, another is the attempt to track down the sources of different components in the air, using source-apportionment methods.

In addition, novel exposure parameters such as active surface and/or the volatile and nonvolatile fractions of particles which can be measured with modern measurement sites, should be used more frequently in epidemiological studies to help establish which characteristics of PM determine the adverse health effects.

Exposure assessment/estimation of individual exposure

Exposure assessment, especially for long-term studies, is still a major challenge as substantial small-scale spatial variation exists in the exposure. Hoek et al. (2008) state in their review that in some settings the within-city contrast may be as large as the between-city contrast and that epidemiological studies need to take these contrasts into account. Current approaches include the use of exposure indicator variables such as distance to major roads. Additionally, dispersion, hybrid and LUR models are now being used and the methods are currently being further developed.

Dispersion models use vehicle emissions, air quality data and meteorological data but need to be calibrated (HEI Panel on the Health Effects of Traffic-Related Air Pollution, 2010). Hybrid models combine personal exposure measurements or time-activity diaries with traffic surrogates or exposure models. In a special report by the Health Effects Institute (HEI), these models were rated as the currently best available method in epidemiological studies on health effects of air pollution (HEI Panel on the Health Effects of Traffic-Related Air Pollution, 2010). LUR models combine air pollution monitoring at a number of selected locations and the subsequent development of stochastic models using predictor variables usually obtained through GIS. The resulting model can then be applied to a large number of unsampled locations in the study area, for example the study participants' homes and/or work places, to estimate their individual exposures (Hoek et al., 2008). The predictor variables differ by study; most commonly, they comprise traffic variables, land cover, altitude, population density and, if applicable, distance to sea. Sometimes, meteorology is taken into account. Monitoring data are derived from either routinely collected data or purpose-designed networks and differ therefore in measured pollutants, number and distribution of monitoring sites as well as temporal resolution (Hoek et al., 2008). Most models have been developed for NO_2, and, to a smaller extend, NO, $PM_{2.5}$ and EC. So far, only one model has been developed for UFP (Hoek et al., 2009). In an 18-month measurement campaign,

UFP were measured for a week at 50 selected locations in the city of Amsterdam and a model was developed for the whole city. Authors concluded that their model had the same validity as previously published studies using more common air pollution markers.

More and more epidemiological studies use LUR models for exposure estimation to examine the association with different health outcomes, for example, regarding reproduction (Aguilera et al., 2009; Brauer et al., 2008; Slama et al., 2007) or respiratory diseases in children (Karr et al., 2009; Morgenstern et al., 2008; Ryan et al., 2007). However, pollution data for the respective study area need to be available to enable the development of a model. Purpose-designed measurement campaigns often yield better data as they can be more densely distributed than routine measuring sites. On the other hand, these measurement campaigns are temporally limited, whereas the routinely measured data are usually continuously available. Care needs to be taken in the selection of routine measuring sites, as they might for example be located at the city's hotspots and not necessarily represent average exposure of the population of a city (Hoek et al., 2008).

To our knowledge, so far only two studies, both of them from Canada, have assessed the correlation between personal exposure and LUR models. Sixty-two pregnant women carried personal samplers for $PM_{2.5}$, NO and NO_2 for 48 h, up to three times during the course of their pregnancy in Vancouver, Canada. Authors reported a moderate correlation for LUR models and personal NO (Nethery et al., 2008). A study in Hamilton, Canada, found that predicted NO_2 exposures from LUR models were not associated with personal NO_2, whereas interpolated surfaces of particulates were modestly associated (Sahsuvaroglu et al., 2009).

Personal exposure measurements

Epidemiological studies still have difficulties in separating health effects of exposure that occur on a personal level from exposures from urban or regional background, because of different microenvironments or activities of an individual, such as time spent in traffic, degree of PM penetration into homes or environmental tobacco smoke exposure (Brook et al., 2010). Indoor air pollutants are still a massive problem in the developing world due to inefficient cooking with biomass indoors and are estimated to be responsible for an health burden of about 2.6% world wide (Balmes, 2010). In industrialized countries, there is also a variety of indoor sources of air pollution such as smoke from candles and wood-burning stoves or fireplaces which can cause adverse health effects (Naeher et al., 2007), but outdoor air pollutants, especially from traffic, are usually the main concern.

Mauderly et al. (2010) state in their commentary on future research needs for the field of health effects of air pollution that one of the greatest limitation in advancing the field further is the uncertainty in respect to personal exposures to multiple, but also to single pollutants. In recent years, more and more studies examine the association between ambient, home outdoor and/or home indoor air pollution for certain pollutants. Brown et al. (2008) for example examined whether ambient site, home outdoor and home indoor concentrations could serve as a proxy for personal exposures to sulfate, $PM_{2.5}$ and EC in a sample of 25 individuals living in the Boston, MA, metropolitan area. They found that correlations for $PM_{2.5}$ and EC were weaker than for sulfate. Local traffic, indoor sources and personal activities mainly affected $PM_{2.5}$ and EC with regard to their association with ambient monitors. Moreover, the correlations differed slightly by season.

A workshop held by the environmental protection agency (EPA) in 2006 dealt with the role and contributions of exposure assessment in addressing the issues of potential errors resulting from the use of a central monitoring site as a proxy for individual exposure to ambient air pollution. A publication by Sarnat et al. (2007) summarizes the main results of this workshop. One possibility of addressing this complex issue is the use of calibration methods in which large amounts of data from one or more fixed monitoring sites are used for calculation of associations between health outcome and air pollution. The associations found are then adjusted using a much smaller amount of data from personal monitors collected at the same time period. However, only few studies have used this approach so far (Dominici et al., 2000; Strand et al., 2006). The challenge of this method is to differentiate between the total personal exposure, which is being measured and the ambient fraction of the personal exposure, which is the actual variable of interest (Sarnat et al., 2007). Some studies make use of time-activity diaries to adjust for the contribution from nonambient sources or use sulfate as a tracer to distinguish between ambient and nonambient sources as suggested by Wilson and Brauer (2006). The basic assumption for most epidemiological studies is that ambient air pollution measured at one central measurement site reflects the background concentration that a person is exposed to, mixing regional and local pollution, while personal exposure represents short-term exposure changes due to personal behavior such as commuting in traffic. Quite a few studies found supporting evidence for the use of ambient monitors as surrogates of population exposures in time-series epidemiological studies especially for $PM_{2.5}$ (Cyrys et al., 2004; Ebelt et al., 2005; Janssen et al., 1998; Janssen et al., 2000; Meng et al., 2005; Sarnat et al., 2000) but also for BS (Cyrys et al., 2004) and PM_{10} (Ebelt et al., 2005). Less is known about the personal-ambient association regarding NO_2 and SO_2 (Sarnat et al., 2007). Studies showed a rather weak correlation between personal and ambient gaseous pollutants and the health effects found in association with NO_2 in some epidemiological studies are questionable. It is conceivable that NO_2 concentrations measured at ambient monitoring sites merely represent a marker for some other pollutant affecting the

population such as $PM_{2.5}$ or other traffic-related particles (Sarnat et al., 2007). Summing up, the authors of the EPA workshop recommend exposure assessment panel studies to collect information on the temporal variability of personal exposure and the correlation between personal and ambient pollutants. In the long run, these studies can help reduce exposure error in the estimation of health risks (Sarnat et al., 2007). Mauderly et al. (2010) also recommend the use of time-activity data together with micro-environmental studies on certain air pollutants to be able to develop models for personal exposures such as the Stochastic Human Exposure and Dose Simulation (Burke et al., 2001; Ozkaynak et al., 2009).

In addition, more epidemiological studies make use of personal air pollution monitors to characterize the participants' personal exposure in addition to the ambient background monitor (Mauderly et al., 2010). One has to keep in mind, though, that much of the variation in personal exposures comes from nonambient sources. Therefore, even personal measurements need to be interpreted with care when they are used to examine an association between a certain health outcome and ambient air pollutants.

Multipollutant models

Although ambient air pollution is encountered as a complex mixture, most epidemiological studies on health effects of air pollution use individual criteria pollutants for the estimation of health effects. Dominici et al. (2010) argue in their commentary for a multipollutant air quality management framework. They state separate air quality standards for criteria pollutants do not account for the health responses associated with the simultaneous exposure of multiple pollutants. Most health burdens associated statistically with individual criteria pollutants are likely to be caused by multiple criteria and noncriteria pollutants and among them, synergisms and antagonisms may occur. Epidemiological studies have only a low power to study such interaction effects, and can only study interactions of pollutants which are actually measured during the course of the respective study. Mauderly et al. (2010) point out that one of the most important current limitations in estimating multipollutant effects is the lack of information regarding personal exposures to multiple pollutants, especially for pollutant classes whose ratios vary strongly between different exposure environments like indoors and outdoors. Moreover, the authors emphasize that the time-scales for health endpoints may vary, depending on the exposure pollutant, a fact, which can complicate things even further if one assumes that pollutants might interact. Some of the primary pollutants also play a role in the formation of secondary pollutants, such as nitrogen oxides, PNC and $PM_{2.5}$ in the formation of ozone through photochemical processes. In addition, independent effects of the single pollutants are hard to estimate due to the interrelationships among them and the fact that many of them stem from common sources such as for example traffic.

One possibility is the use of factor analysis or principal component analysis to group the various measured pollutant into independent groups. In a second step, health effects of these groups can be assessed rather than that of single pollutants. In addition, further development of statistical methods such as the lasso or statistical search variable selection, which removes spurious predictors in the model and group highly correlated predictors, is needed (Dominici et al., 2010). Other approaches on how to examine multipollutant models in epidemiological studies include a detailed characterization of the multiple pollutants in one place over time, especially with regard to temporal-spatial variations of these pollutants and multi-city approaches, if cities differ in sources and concentrations of pollutants. Moreover, the use of biologically based markers for criteria and noncriteria pollutants might be helpful (Mauderly et al., 2010).

8.4. Summary

Summing up, there are still open questions in the field of health effects of air pollution. One issue is the lack of knowledge regarding health effects of UFP. Furthermore, studies need to disentangle the impact of single pollutants in the complex pollutant mixture that ambient air pollution consists of. The scientific methods also need further development, especially regarding the estimation of individual exposure to ambient air pollution.

With the aim of advancing beyond the current knowledge in the field of air pollution health effects, Mauderly et al. (2010) mention some key issues in research that should be addressed. In brief, they argue for mobile monitoring programs to improve understanding of temporal and spatial variation of pollutants, conducting time-activity surveys and exposure studies to gain insight into the contributions of indoor and outdoor pollutants to the personal exposure of an individual, or for certain subpopulations. Moreover, they recommend an extended number of air pollutants to be measured as well as the development of biomarkers for criteria pollutants, to facilitate reconstructing exposure-dose-response relationships.

In addition to better assess exposure, the knowledge of health impacts needs to be advanced. The collection of data on an individual level should be intensified, despite being more expensive, to get a better idea of the length of exposure or certain windows of susceptibility e.g., during childhood or pregnancy. Furthermore, more effort needs to be put into the research of exposure—response functions and biological mechanisms (Mauderly et al., 2010). Although quite a number of modes of action have been suggested (see section 7), these were partly substantiated by toxicological and epidemiological studies unresolved issues remain. In addition, the knowledge how long it takes for a certain exposure to cause measurable health effects and also the subgroups of the population that are most susceptible needs to be extended.

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