HEALTH EFFECTS ASSOCIATED WITH AMBIENT AIR POLLUTION

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Dr Jason J. Bonnici,
M.D., MMCFD, Dipl. Fam. Prac. (MCFD)

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Introduction

Ambient air pollution is an established cause of morbidity and mortality, like tobacco smoke. Even more than passive smoking, air pollution is not a lifestyle choice but a ubiquitous involuntary environmental exposure, which can affect 100% of the population, from womb to death.

The first studies conducted to evaluate a possible association between air pollution and mortality date back to the serious events that occurred in the Mosa Valley, Belgium (1930), in the small city of Donora, Pennsylvania ("killer fog" incident of 1948) and in London, United Kingdom (where more than 4000 people were killed in 4 days in December 1952). The latter episode led to the introduction of air pollution control policies.
Despite legislation, leading to dramatic decreases in levels of air pollution, a large body of epidemiological evidence has demonstrated that **pollution continues to have adverse effects on human health**.
Subsequently numerous epidemiological studies have confirmed that **short-term exposure to air pollution** is related to **morbidity and mortality** and that **chronic exposure to air pollution** is associated with **several health outcomes**.
Until the 1990s, population studies focused mainly on **respiratory health**, as the **airways are the primary gateway** for pollution to the human body. The principal epidemiological studies, e.g. the **National Mortality, Morbidity and Air Pollution Study with data from 90 United States cities**, and **APHEA-1 (Air Pollution and Health, a European Approach) and APHEA-II, in 15 and 34 European cities respectively**, begun in the 1990s. These first examined the respiratory effects of atmospheric pollution.
Subsequently the **systemic effects** of pollution became known and the way pollution affects the cardiovascular system was recognised. The epidemiological studies then focused on how pollution peaks affected cardiovascular risk.

There are nowadays **a number of health outcomes** for which there is at least some evidence of an association with air pollution.

1. **Acute Effects:**
    a. daily mortality,
    b. respiratory hospital admissions,
    c. cardiovascular hospital admissions,
    d. emergency room visits for respiratory and cardiac problems,
    e. primary care visits for respiratory and cardiac conditions,
    f. use of respiratory and cardiovascular medications,
    g. days of restricted activity,
    h. work absenteeism,
    i. school days missed,
    j. self-medication,

k. avoidance behaviour,
l. acute symptoms,
m. physiological changes, e.g. in lung function.

2. **Chronic Effects:**
    a. mortality from chronic cardiorespiratory disease,
    b. chronic respiratory disease incidence and prevalence (asthma, COPD),
    c. chronic change in physiological function (e.g. lung function),
    d. lung cancer,
    e. chronic cardiovascular disease

3. **Other Effects:**
    a. low birth weight,
    b. pre-term delivery,
    c. adversely affected cognitive development in infants

Components of ambient air pollution

Ambient air pollution is a ubiquitous and complex exposure. Major pollutants produced by human activity are:

Sulphur oxides/Sulphur dioxide	SO_x/SO_2
Nitrogen oxides/ Nitrogen dioxide	NO_x/NO_2
Carbon monoxide	CO
Carbon dioxide	CO_2
Volatile Organic Compounds	VOCs
Particulate Matter	PM
Ammonia	NH_3
Lead	Pb
Persistent Organic Pollutants	POPs
Ozone	O_3

On one hand, it is to be noted that the health effects of pollution are likely to be caused by a range of pollutants rather than by single constituents of the mixture. On the other hand, among all air pollutants, particulate matter is the type of air pollution that causes the most numerous and serious effects on human health, because of the broad range of diverse toxic substances it contains.

The following **Particulate Matter fractions** are commonly defined, based on their aerodynamic diameter, as:
- **TSP (Total Suspended Particles)** including all particles up to 30 um in diameter;
- **PM_{10}**, with a diameter of <10um
- **Coarse particles**, with a diameter of 2.5 – 10 um
- **$PM_{2.5}$ or "fine particles"** with a diameter < 2.5 um. Fine particles are derived primarily from **direct emissions from combustion processes**, such as power generation and vehicle use of gasoline and diesel. Fine particles also consist of **transformation products**, including sulphate and nitrate particles, which are generated by conversion from primary sulphur and NOx emissions and secondary organic aerosol from VOCs emissions.
- **Ultrafine (UF) particles or $PM_{0.1}$** with a diameter of < 0.1 um (typically in the range of 1-100 nm). UF particles are typically **fresh emissions from combustion-related sources**, such as vehicle exhaust, and atmospheric photochemical reactions. Primary UF particles have a very short life (minutes to hours) and grow rapidly through coagulation and/or condensation to **form larger complex aggregates in the $PM_{2.5}$ range**.
- **Nanoparticles** cover the same size range as UF but the term is more commonly used for engineered material rather than ambient PM.

Single pollutants and their health effects

A consequence of the complexity of air pollution is that its health effects are also complex ranging across numerous and unspecific ailments.
The nose and lungs are where pollution first comes into contact with the human body. Depending on

- the **physical and chemical characteristics** of the pollutants,
- the **anatomical or physiological state** of the person and
- the **breathing pattern or level of activity** of the person,

pollutants may impact at various depths within the respiratory system.

Coarse particles affect the upper airways in particular, while fine particles reach the smaller airways and alveoli, although they are also deposited in the nose.
Water-soluble gases, e.g. SO_2, react with the mucus layer of the upper airways, while less soluble gases, e.g. NO_2, are more likely to reach the alveoli.
Various toxicological and human studies suggest that fine particles may play a dominant role in affecting human health. Their toxicity may be due to sulphates, nitrates, acids and metals. From a number of studies, some of the metals bound to PM_{10} include aluminum, iron, strontium, magnesium, silicon, arsenic, barium, zinc, copper, and cadmium; some of the metals bound to $PM_{2.5}$ include magnesium, iron, strontium, arsenic, cadmium, zinc, aluminum, mercury, barium, and copper. The various chemicals adsorbed onto the surfaces of PM may be relevant at **all size fractions**. Unlike larger particles, $PM_{2.5}$ typically **reach the small airways and alveoli**. The fine fractions also remain suspended for longer periods of time, and are thus **transported over much longer distances** and penetrate more readily into indoor environments.
New studies also suggest that UF particles may be more likely than larger particles to **directly translocate from the lung to the blood** and other parts of the body, giving them possible particular relevance for **cardiovascular outcomes**.
The role and sources of coarse particles have been less investigated but more recent studies confirm that adverse health effects are associated with this size fraction too.
Both emission- and air quality-based policy approaches focus on single pollutants; however health effects are likely to be the result of concurrent exposures to complex mixtures. **In fact, the current epidemiological and toxicological literature provides no evidence that any single pollutant or source is responsible for the full range of observed health effects.** For example, the associations between daily mortality rates and both ozone and PM appear to be stronger when both pollutants are present.

Pathophysiology

General pathophysiological effects of inhaled pollutants

Particles <10um, SO_2, NO_2 and ozone penetrate to the trachea and bronchi.
There they cause:

- irritation of mucous membranes, local inflammation, changes in mucous compounds, immigration of inflammatory and immune defence cells;
- impairment of cilia activity, impairment of epithelial clearance, e.g. of upward transport of particles, bacteria, etc;
- constriction of bronchi through muscular spasm and swelling of mucosa.

Particles <2-3um, NO_2 and ozone penetrate to the pulmonary alveoli.
There they cause:

- impairment of ability of immune cells to ingest and dissolve foreign material and debri;
- local inflammation, change in permeability of cell membranes;
- transfer of inflammatory proteins and of ultrafine particles in the pulmonary tissue and the circulation

Ultrafine Particles <0.1um penetrate to the pulmonary tissue and into the circulation.
There they cause:

- inflammation in endothelia of blood vessels, enhanced formation of plaques, coagulation, thrombosis.

Postulated Mechanism of effects

A great number of a range of studies have brought forward postulated mechanisms for the found health impacts of ambient air pollution:

- A range of experiments focus on the ability of ambient particles to induce redox cycling, confirming the contribution of PM to oxidative stress as a relevant pathway for a broad range of health effects. **Oxidative stress is suggested as the main mechanism leading to local and systemic inflammation following inhalation of pollutants**.
- Animal studies revealed that rabbits, mice or rats chronically exposed to concentrated ambient particles **develop atherosclerosis**.
- Human chamber studies observed **greater allergic inflammation** among sensitized subjects exposed to both allergens and diesel particles compared with those exposed to allergen alone. The adjuvant effect of diesel particles was particularly strong among subjects with a deficiency in two genes relevant in the antioxidant defence in the airways, namely the gluthatione transferases GSTM and GSTP.

General pathophysiological effects of pollutants on the cardiovascular system

A number of physiological processes are examined to pathologically link air pollution with cardiovascular effects:

enhanced coagulation/thrombosis.

The principal pollutant currently identified as responsible for prothrombotic effects is particulate matter. Exposure to wood smoke increased the levels of serum amyloid A, a cardiovascular risk factor, as well as factor VIII in plasma and the factor VIII/von Willebrand factor ratio.

UFPs and accumulation mode particles are associated with an immediate increase in plasma sCD40L, also known as CD154, a marker for platelet activation that can cause increased coagulation and inflammation.

$PM_{2.5}$ and O_3 also exert prothrombotic effects. Higher ambient air concentrations of PM_{10}, CO and NO_2 are associated with a shorter Prothrombin time, suggesting a tendency towards hypercoagulability after short-term exposure to air pollution.

altered cardiac autonomic function with a propensity for arrhythmias

Decreased Heart Rate Variability has been linked with exposures to PM_{10}, $PM_{2.5}$, NO_2, SO_2, O_3 and coarse particles. Elderly patients seem to be more susceptible. Additionally, in normal youngsters $PM_{2.5}$ accumulative exposure showed a significant negative association with the percentage of differences between adjacent normal RR intervals larger than 50 ms (pNN50). Spectral analysis of R-R intervals after SO_2 exposure was associated with an increase in total power (TP) and high (HF) and low frequency (LF) power in normal subjects.

UFPs, NO_2 and CO were at lags of 0-2 days consistently and significantly associated with decreased low-to-high frequency ratio (LF/HF), a measure of sympathovagal balance, in a large multicenter study of elderly subjects.

Particulate air pollution seems to have an immediate effect on repolarization duration, morphology, and variability representing myocardial substrate and vulnerability, key factors in the mechanisms of cardiac death.

acute arterial vasoconstriction.

Short-term inhalation of fine particulate air pollution and ozone at concentrations that occur in the urban environment causes acute conduit artery vasoconstriction.

Inhalation of diesel exhaust causes an immediate (within 2 hours) and sustained (up to 24 hours) impairment of vascular and endothelial function in man due to a selective and persistent impairment of endothelium-dependent vasodilatation that occurs in the presence of mild systemic inflammation. Diesel exhaust increased plasma cytokine concentrations (tumor necrosis factor-alpha and interleukin-6) but appeared to reduce acetylcholine and bradykinin induced forearm vasodilatation.

Particulate Matter may activate the angiotensin type 1 receptor (AT1R), a G protein-coupled receptor that regulates inflammation and vascular function. Urban particles activated extracellular signal-regulated kinases 1 and 2 (ERK1/2) and p38 mitogen-activated protein kinases (MAPKs) in human pulmonary artery endothelial cells. Urban Particles at 1-100 microg/mL induced acute vasoconstriction in pulmonary artery. Urban

Particles also produced a time- and dose-dependent increase in phosphorylation of ERK1/2 and p38 MAPK.

pulmonary and systemic inflammatory responses

$PM_{2.5}$ and O_3 are responsible for proinflammatory effects, firstly localized in the lungs, but then become systemic.

PM_{10} may interact with cigarette smoking and increase plasma homocysteine in healthy subjects. Mild hyperhomocysteinemia is independently associated with an increased risk of cardiovascular disease.

Increases in accumulation mode particles, UFPs and PM_{10} exposure caused increased levels of C-reactive protein in males with coronary heart disease, with a 2-day delayed response.

In healthy subjects, inhalation of elemental carbon UFPs alters peripheral blood leukocyte distribution and expression of adhesion molecules, in a pattern consistent with increased retention of leukocytes in the pulmonary vascular bed.

the chronic promotion of atherosclerosis

Carbon Black, a component of diesel exhaust particles, directly affects the endothelium, causing cytotoxic injury (such as cytosolic vacuole formation, cell disorientation and decreased density), inflammatory responses, and inhibition of cell growth. It induced monocyte chemoattractant protein-1, reduced the expressions of connexin37 and endothelial nitric oxide synthase and induced pro-inflammatory molecules. Endothelial cell injury/inflammation and membrane disintegration are related to the initiation of atherosclerosis, and Nitric Oxide is anti-atherogenic and anti-thrombogenic.

$PM_{2.5}$ was associated with an increase in the carotid intima-media thickness, a measure of subclinical atherosclerosis.

Oxidative Stress

The physical characteristics and the chemical composition of PM play a key role in reactive oxygen species generation in vitro and in vivo. According to the hierarchical oxidative stress hypothesis, antioxidant phase II enzymes protect against PM-induced inflammation and cytotoxicity.

Exposure to wood smoke increased urinary excretion of free 8-iso-prostaglandin2alpha, a major F2-isoprostane; this indicates a temporary increase in free radical-mediated lipid peroxidation, inducing oxidative stress.

Transition metals, including iron, bound to ambient particles and the related oxidative stress may play an important role in cardiac toxicity of particles.

Postulated Mechanism of Effects

Evidence is accumulating in support of two mechanistic hypotheses:

- inhalation of pollutants might provoke a **local inflammatory response** with the consequent release into the circulation of pro-thrombotic and inflammatory cytokines. A **systemic response** of this nature would put individuals with coronary atheroma at increased risk of cardiac events;
- exposure to pollutants may have an **adverse effect on cardiac autonomic control**, leading to an increased risk of arrhythmia in susceptible patients.

Susceptibility to Health Effects

In any given population, susceptibility to adverse effects of air pollution is expected to **differ widely between people, and within the same person**, over time.
For example, while the least susceptible may experience no symptoms at all or only clinically irrelevant changes, similar exposure may trigger serious exacerbations of health problems among the frail.
Similarly, some asthmatics may suffer attacks once air pollution increases while other asthmatics remain stable.

Susceptibility Factors
While some factors modify the level of exposure, other characteristics may determine how an individual will be affected by exposure to ambient air pollution:

- the **increase in ventilation rate during physical activity results in higher exposure** to pollutants. This is important for people who exercise to keep fit or to decrease weight or as part of their therapy for various medical conditions. Depending on where people engage in physical activity, they may face a trade-off between the health benefits of the activity and higher exposure to toxicants.
- As a general rule, **children are more affected due to their relatively higher ventilation and metabolic turnover** during childhood and adolescence.
- some studies suggest that **genetic deficiencies in the detoxification of xenobiotics**, such as the null variant of glutathione S-transferase Mu 1, amplify the adverse effects of ambient air pollution.
- **Pre-existing diseases** may determine susceptibility. This is particularly well established for the acute effects of ambient air pollution.
    - e.g. air pollution can cause exacerbations among **people with asthma or Chronic Obstructive Pulmonary Disease**;
    - e.g. people who suffer from **ischaemic heart disease or atherosclerosis** may suffer a heart attack or stroke after exposure to ambient air pollution;
    - e.g. a few studies have shown **diabetics** to be more strongly affected by acute cardiovascular effects of ambient air pollution.
    - e.g. experimental studies indicate that **obesity and diabetes (situations of chronic subclinical systemic inflammation)** are associated with stronger effects of air pollution.

High-Risk Groups for cardiovascular effects of ambient air pollution

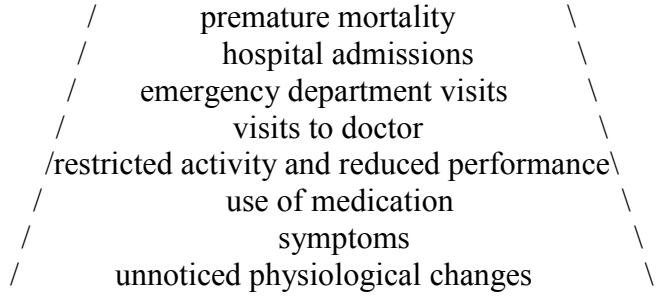
- Smokers: Although smoking is a much larger risk factor for cardiovascular disease mortality, exposure to fine PM imposes additional effects that seem to be at least additive to if not synergistic with smoking.
- Elderly (>/= 65 years of age): There are significant associations of CO, NO_2 and PM with adult cardiovascular hospital admissions for cardiac failure, ischaemic heart disease and myocardial infarction, possibly at lower pollution levels than for the general population. There are also significant associations of ambient sulfate and ozone with supraventricular

dysrrhythmia; and additionally a statistically significant synergistic effect between O_3 and temperature for cardiovascular mortality.

- Patients with pre-existing coronary heart disease or hypertension: Studies show significant association between air pollution and cardiovascular morbidity and mortality, particularly $PM_{2.5}$ and PM_{10}. Elderly participants reporting cardiovascular conditions (for example, previous myocardial infarction or hypertension) were the most susceptible to sulfate and ozone pollution induced Supraventricular Ectopics. There is evidence of stronger associations of dysrhythmia and congestive heart failure visits with comorbid hypertension in relation to increased air pollution levels (PM_{10}, NO_2 and CO) compared with visits without comorbid hypertension. Other studies show that elevated concentrations of NO_2, $PM_{2.5}$ and UFPs increased the risk of arrhythmia (supraventricular and ventricular tachycardia) in men with coronary heart disease.
- Diabetes: Diabetics with and without cardiovascular disease may be susceptible to the short-term effects of air pollution, including $PM_{2.5}$, PM_{10}, NO_2 and CO.
- COPD: Patients with COPD are more susceptible to adverse cardiovascular events associated with ambient air pollution, whether NO_2, CO, PM_{10} and O_3.
- People exercising in environments pervaded by air contaminants ($PM_{2.5}$ and UFPs) are probably at increased risk, due to an exercise-induced amplification in respiratory uptake, lung deposition and toxicity of inhaled pollutants.

The Pyramid of Health Outcomes

Air pollution epidemiology has shown a broad range of health outcomes, ranging from minor changes to mortality: unnoticed physiological changes, symptoms, use of medication, restricted activity and reduced performance, visits to doctor, emergency department visits, hospital admissions and premature mortality.
This range is depicted as a pyramid, with the **number of people affected by the most extreme effects being much smaller than those affected by less severe outcomes**.
The coherence of results observed across this broad range of interrelated outcomes provides a very strong argument for a causal role of pollution on public health.



Short-term Health Effects of Ambient Air Pollution

Increased daily mortality from cardiovascular and respiratory diseases:

Typically, the acute effects of ambient air pollution are particularly small. A large body of studies, for instance, indicates that a 10ug/m^3 increase in daily ambient $PM_{2.5}$ is associated with a 0.5-1.0% increase in daily mortality, corresponding to an extremely small, but highly significant and relevant, relative risk of 1.005-1.010.

A large number of epidemiological studies have shown that the **daily mortality, mainly from cardiovascular and respiratory diseases, follows the daily fluctuation of air pollution.**
For example, the **APHEA analysis** carried out in 29 mostly European study centres found an **increase of deaths from illness of 0.6% per 10ug/m^3 increase in PM_{10} concentration** (mean of the day of death versus the day before). **Deaths from cardiovascular diseases increased by 0.7%.**
For example, the **CALFINE analysis from 9 heavily populated California counties** revealed associations of $PM_{2.5}$ levels with several mortality categories. **Specifically, a 10-ug/m^3 change in 2-day average $PM_{2.5}$ concentration corresponded to a 0.6% increase in all-cause mortality**, with similar or greater effect estimates for several other subpopulations and mortality subcategories, including respiratory disease, cardiovascular disease, diabetes, age >65 years, females, deaths out of the hospital, and non-high school graduates.
These results are similar to those of a previous meta-analysis conducted on behalf of the World Health Organisation, which found the same effect size for **total mortality (0.6% per 10ug/m^3 increase in PM_{10} concentration)** and a slightly higher effect size for **cardiovascular deaths (0.9% per 10ug/m^3 increase in PM_{10} concentration)**.

Increased hospital admissions from cardiovascular and respiratory diseases:

APHEA found an increase in **cardiac admissions of 0.7% per 10ug/m^3 increase in PM_{10} concentration**.
APHEA also found an **increase in respiratory admissions**. The increases were:

- 1.2% for asthma in children;
- 1.1% for asthma in adults aged up to 64 years; and
- 0.9% for all respiratory diseases (including COPD, asthma and other respiratory diseases) in the elderly.

In studies of COPD, asthma and respiratory admissions, **coarse PM has a stronger or as strong short-term effect as fine PM**, suggesting that coarse PM may lead to adverse responses in the lungs triggering processes leading to hospital admissions. There is also support for an association between coarse PM and cardiovascular admissions.

Increased hospitalization for cardiovascular causes

Hospital admissions for cardiovascular disease were positively correlated to particles, SO_2, NO_2, O_3 and CO in a number of European cities.
PM_{10} was significantly associated with admissions for congestive heart failure and admissions for total cardiovascular diseases. In the Spanish study, effects were higher among female group for most of the analyzed outcomes.
In a study of 204 US urban counties (population >200,000) with 11.5 million Medicare enrollees (aged >65 years) **$PM_{2.5}$ was significantly associated with admissions for primary diagnosis of cerebrovascular, peripheral, and ischemic heart diseases, heart rhythm and heart failure**. The largest association was for heart failure.

Acute Myocardial Infarction

Acute myocardial infarction (AMI) is the leading cause of death attributed to cardiovascular diseases. An association between traffic related air pollution and AMI has been suggested. The principal causal polluter is not clear.
Particulate air pollution appears to increase susceptibility to myocardial ischaemia.
In a study using observational data short-term O_3 exposure within a period of 1 to 2 days is related to acute myocardial infarction in middle-aged (55-64 years of age) adults without heart disease, whereas NO_2 and SO_2 are not.
A study in 2 French cities shows that at a 5 day lag the association between NO air pollution and myocardial infarction was statistically significant, for O_3 a weak positive association was found but for CO, SO_2, and particulate matter no association was found.

Cardiovascular Mortality

Studies show that **NO_2 had a significant positive association** with daily mortality, all causes and cardiovascular.
Other studies show that **O_3 was associated with cardiovascular daily mortality** and there is evidence for a statistically significant synergistic effect between O_3 and temperature for cardiovascular mortality, particularly in elderly people.
SO_2 was associated with a statistically significant increase of mortality from all causes, including cardiovascular in studies researching the Polish cities of Krakow, Lodz, Poznan and Wroclaw, in Beijing, China and in the APHEA projects.
PM was significantly associated with cardiovascular mortality. $PM_{2.5}$ was associated with several mortality categories including cardiovascular disease.
Exposure to combustion-derived air pollution is associated with an early (1-2 hours) and sustained (24 hour) rise in cardiovascular morbidity and mortality. The daily mean coarse fraction ($PM_{10-2.5}$) was associated with increased cardiovascular mortality.

Exacerbations in susceptible people.

People are not affected equally by ambient air pollution.
People with asthma, especially children without anti-inflammatory or bronchodilator therapy, suffer more on or after days with higher pollution levels. Panel studies on asthmatics have found increased wheezing, cough and attacks of breathlessness, accompanied by a lower lung function and need of additional relief medication, associated with daily variation in levels of PM and NO_2.

Long-term Health Effects of Ambient Air Pollution

In the past 10 years many studies have confirmed the adverse effects of even moderate levels of air pollution. The levels of ambient air pollution previously thought to have no effect on health have been found to impact health, and the latest levels recommended by the World Health Organisation are lower than they used to be in the previous decade and lower than what is legislated for in the European Union..

Air Pollution and Life Expectancy

While death is in itself an acute event, life expectancy and time to death are the result of both acute and chronic pathologies.
Several cohort studies have estimated losses or gains in life expectancy related to changes in air quality. **Estimates include reductions in life expectancy of 1.11 years in the Netherlands, 1.37 years in Finland and 0.80 years in Canada resulting from increases in ambient $PM_{2.5}$ concentrations of 10ug/m^3.**
An ecological study investigated the **association between life expectancy across the USA and changes in the community-level air quality.** This study produced **very similar results** to cohort studies, **attributing a 7-month gain in life expectancy to a 10 ug/m^3 improvement in ambient $PM_{2.5}$ concentration.**
Studies conducted in Europe, USA and Canada all confirm that the **overall effects of pollution on mortality are far larger than the fraction attributed to acute exposures**.
Cardiopulmonary mortality (i.e. respiratory and cardiovascular disease contributing to mortality) was associated with long-term differences in PM and sulphate concentrations between cities in the **Harvard Six Cities Study** and in the **American Cancer Society study**.
Comparison of community-level concentrations of fine PM with death rates among more than 500,000 participants in the **American Cancer Society** study showed **a 6% increase in cardiopulmonary deaths 16 years later per 10ug/m^3 of $PM_{2.5}$.** The estimate for **total mortality was 4%**. The range of the lowest to highest long-term average $PM_{2.5}$ concentration across communities was only up to three-fold and **the risk of death during follow-up varied by 10-15% across the range (the Relative Risks were 1.10 to 1.15)**.
As expected, **heavy smokers,** as compared with never-smokers, had a larger risk of death during follow-up, with **Relative Risks exceeding 2.0**. Due to the large sample size, the findings related to air pollution were **clearly statistically significant**.
In a reanalysis of 18 years of **American Cancer Society follow-up from the Los Angeles area**, with improved exposure assignment to each residence, the estimates were higher. **Cardiopulmonary mortality increased by 20% and death due to ischaemic heart diseases by 49% per 10ug/m^3 increase in $PM_{2.5}$.** Many other cohort studies exist from the USA showing an association with mortality.

Respiratory Health in Children

Children are more susceptible to the effects of air pollution than adults, for several reasons:

- They are more active and have more outdoor activities.
- they breathe faster and their metabolic rate is higher than adults'.
- their immune systems are not fully developed, so the incidence of respiratory infections is high.

Several cross-sectional studies from Germany, Switzerland, France and the USA found as early as the 1980s that **school-age or pre-school children in communities exposed to higher levels of dust, SO_2 and NO_2 suffered more from cough and acute bronchitis** compared with children in less polluted region.

More recently, many cross-sectional studies have reported **lower lung volumes in children living in more polluted areas.** It is likely that a child suffering a pollution-related lung function deficit will continue to have less healthy lungs throughout his/her life.

Large amounts of data are available about the development of asthma in children as a function of proximity to traffic. For example, the **Californian Children's Health Study** gave strong evidence that **traffic-related pollutants contribute to the development of childhood asthma**, at least among children who are genetically susceptible.

A review of the studies of the evidence for the possible impact of ambient air pollution on the fetus and the infants (i.e. less than 1 year of age) published during the decade, 1994--2003, showed an outstanding consistence in the magnitude of the effects, despite the different designs used. As a whole, data show that **an increase in 10 ug/m^3 of PM_{10} is associated with about 5% increase in post-neonatal mortality for all causes and around 22% for post-neonatal mortality for respiratory diseases**.

Regarding damage in foetal health, although results are not always consistent, most studies show associations with exposure to air pollution during pregnancy. However, the precise mechanisms of action of air pollutants on adverse reproductive results are still unknown, so is the period of exposure most relevant during pregnancy and the specific pollutant which may represent a higher risk.

Respiratory Health in Adults

Chronic cough and phlegm as well as lung function decrement have been associated with long-term ambient inhalable PM exposure in several repeated cross-sectional studies in the USA and Europe.

A number of studies give evidence of **an association of several correlated gaseous and particulate pollutants, including ozone, NO_2, CO, PM, and organic carbon, with specific respiratory conditions**, such as upper and lower respiratory tract infections, pneumonias, exacerbations of Chronic Obstructive Pulmonary Disease and exacerbations of asthma.

A few studies have supported the notion that air pollution itself **contributes to Chronic Obstructive Pulmonary Disease**.

Epidemiological studies of air pollution and lung function reveal **a difference of a few per cent in lung function for a difference in exposure of, for instance, 10ug/m^3 in fine particle concentrations**. This represents **an overall "leftward" shift in the distribution of lung function** occurring in populations with higher levels of exposure i.e. an increase in the number of people with clinically relevant decrements in lung function. This results in an increase in the number of people with pathological degrees of lung function deficit, with the concomitant increase in morbidity, costs and premature mortality.

Cardiovascular Health

In recent years, the **main focus of pollution research has shifted from respiratory to cardiovascular diseases,** because the associations between air pollution and cardiovascular health appear to be stronger than first thought.
A cross-sectional study in Germany found an effect of traffic on the prevalence of coronary heart disease independent of $PM_{2.5}$ (Heinz Nixdorf RECALL study), where myocardial infarction, stent and bypass interventions were more prevalent in people living close to high concentrations of road traffic.
The most important pathology in cardiovascular disease is atherosclerosis. Atherogenesis, the development of atherosclerosis, is the result of a long-term process. Studies conducted in animals gave the first evidence of a link between pollution and atherogenesis: the **animals developed atherosclerosis after long-term exposure to concentrated urban PM**. Moving on to human studies, a study in Germany found that a **50% reduction in the distance between subject's residence and the nearest major road was associated with a 7% higher calcification score**, independent of background $PM_{2.5}$ levels.

Cardiovascular Mortality

Fine Particulate Matter is associated with increased risk of cardiovascular mortality; in some studies the association was most strong with mortality attributable to ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest, and comparable or larger risks are observed for smokers relative to nonsmokers.
$PM_{2.5}$ and PM_{10} were associated with increase in the risk of death from cardiovascular disease Gaseous pollution, like CO, SO_2 and NO_2 had an effect on cardiovascular causes of death in both younger and older age groups.
Cardiovascular causes seemed to have threshold effects in some studies and a linear relationship in most studies.
A systematic review of **all studies published between 1950 and 2007** of associations between long-term exposure to ambient air pollution and the risks in adults of non-accidental mortality and the incidence and mortality from cancer and cardiovascular and respiratory diseases showed that **long-term exposure to $PM_{2.5}$ increases the risk of non-accidental mortality by 6% per a 10 ug/m^3 increase**, independent of age, gender, and geographic region. Exposure to $PM_{2.5}$ was also associated with an **increased risk of total cardiovascular mortality of 12-14% per a 10 ug/m^3 increase in $PM_{2.5}$**.

Cardiovascular mortality was associated with living near a major road and, less consistently, with the estimated ambient background concentration in a study of 5,000 people participating in the Netherlands Cohort study on Diet and Cancer, (age 55-69 years) from 1986 to 1994.
O_3 was significantly associated with cardiovascular mortality in the cold season but not in the warm season in a study in Shanghai, China.

Coronary Heart Disease
Traffic related air pollution, in a study of 3,399 participants from two German cities, is significantly associated with prevalence of Coronary Heart Disease. Subgroup analysis showed stronger effects for men, participants younger than 60 years and never-smokers.
$PM_{2.5}$ was associated with an increase in the risk of a cardiovascular event in a study of 65,893 postmenopausal women without previous cardiovascular disease in 36 U.S. metropolitan areas from 1994 to 1998.

Acute Myocardial Infarction
CO and UFPs are associated with a first Acute Myocardial Infarction in the three European cities of Helsinki, Rome and Stockholm; effects of air pollution were more pronounced during the warm than the cold season.
Long-term average air pollution exposure was associated with an increased risk of fatal AMI, especially for out-of-hospital death, but not with overall AMI, in a case-control study in Stockholm county in 1992 to 1994. NO_2, CO, and PM_{10} were used as indicators of traffic emissions and SO_2 as an indicator of emissions from residential heating.

Cardiovascular Hospitalizations
PM, NO_2 and CO were significantly associated with cardiovascular disease hospitalizations. Changes in ozone concentrations were not significantly associated with any disease outcomes.

Lung Cancer

Based mostly on experimental and occupational data, the International Agency for Research on Cancer has evaluated:

- benzene, benzo(a)pyrene, 1,3-butadiene and Polycyclic Aromatic Hydrocarbons (PAH) containing soot as carcinogens for humans (group 1);
- diesel engine exhaust and other hydrocarbons as probably carcinogenic to humans (group 2A); and
- gasoline engine exhaust as possibly carcinogenic to humans (group 2B).

The California Environment Protection Agency also considers diesel exhaust to be carcinogenic.
In the **American Cancer Society cohort study, lung cancer incidence increased by 8% per 10 ug/m^3 increase in $PM_{2.5}$ levels** measured as between-city difference.
A systematic review of **all studies published between 1950 and 2007** of associations between long-term exposure to ambient air pollution and the risks in adults of non-accidental mortality and the incidence and mortality from cancer and cardiovascular and

respiratory diseases showed that **long-term exposure to $PM_{2.5}$ was associated with an increased risk of mortality from lung cancer (range: 15% to 21% per a 10 ug/ m^3 increase)**.
In a Norwegian cohort study lung cancer incidence increased by 11% per 10 ug/m^3 increase in NO_x from traffic.
However not all long-term epidemiological studies have shown a link between ambient air pollution and lung cancer risk.

Reproductive Outcomes

A review of studies on low birthweight, intrauterine growth retardation and pre-term birth concluded that the **evidence for an adverse effect of PM pollution was still inconsistent**. Since then, several large registry studies in the USA, Canada and East Asia have found associations of fetal growth and duration of pregnancy with traffic-related pollutants, and **less consistently with $PM_{2.5}$**.

Neurodevelopment, Neurodegeneration and Traffic Pollution

Ultrafine particles from combustion processes have been shown in animals to translocate from the nose through the olfactory nerve to the brain, resulting in inflammatory processes resembling degenerative diseases.
A Mexican research team observed more brain inflammation and accumulation of amyloid in post mortem examination of individuals from areas with heavy air pollution compared with individuals from areas of better air quality. Intelligence score has also been shown to be lower in children with higher PAH exposure in pregnancy. However, in these studies all exposure indicators were strongly correlated with social indicators as education and race of mothers, income and noise exposure, and the cohorts had high dropout rates. Therefore, **it is not yet possible to conclude that these effects are truly the consequence of ultrafine particles**.

The Burden of Disease

Alteration of the air we breathe, due mainly to the environment being transformed by the activities of humans, is a increasing cause of concern for physicians, public health decision makers and governmental agencies responsible for environmental protection because the modifications of air composition have a proven harmful effect on health and provoke symptoms, predominantly respiratory but also dermatological and cardiac.

As part of the World Health Organization (WHO) Global Burden of Disease Comparative Risk Assessment, the burden of disease attributable to urban ambient air pollution was estimated in terms of deaths and disability-adjusted life years (DALYs).
Air pollution is associated with a broad spectrum of acute and chronic health effects, the nature of which may vary with the pollutant constituents.
Particulate air pollution is consistently and independently related to the most serious effects, including lung cancer and other cardiopulmonary mortality.
Ambient air pollution, in terms of **fine particulate air pollution ($PM_{2.5}$), causes**:

- about 3% of mortality from cardiopulmonary disease,
- about 5% of mortality from cancer of the trachea, bronchus, and lung, and
- about 1% of mortality from acute respiratory infections in children under 5 years,

worldwide. This amounts to about **0.8 million (1.2%) premature deaths and 6.4 million (0.5%) years of life lost**. This burden occurs predominantly in developing countries; 65% in Asia alone.
These estimates consider only the impact of air pollution on mortality (i.e., years of life lost) and not morbidity (i.e., years lived with disability). If air pollution multiplies both incidence and mortality to the same extent (i.e., the same relative risk), then the DALYs for cardiopulmonary disease increase by 20% worldwide.
A significant attempt to estimate, on an annual basis, the negative effects of air pollution from PM_{10} has been carried out on data from Austria, France, and Switzerland. For example, **in France, air pollution from PM_{10} is responsible annually** for:

- 31,700 deaths in adults,
- 36,700 new cases of chronic bronchitis in adults
- 577,000 attacks of asthma in adults,
- 450,000 cases of acute bronchitis in children and
- 243,000 attacks of asthma in children.

A study on the long-term effects of air pollution on about 500,000 residents in metropolitan US areas evidenced that **each 10 ug/m^3 elevation in fine particulate air pollution is associated** with:

- approximately a 4% increased risk of all-cause mortality,
- approximately a 6% increased risk of cardiopulmonary mortality, and
- approximately an 8% increased risk of lung cancer mortality.

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Studies from Malta

A number of medical studies in the Maltese Islands have looked at the health impacts on the population living around major environmental polluters.
The studies referenced for this document are:
- ISAAC study Phase I (1994);
- ISAAC study Phase III (2001/2);
- ECRHS in Fgura and Zejtun (2001);
- Increased prevalence in asthma-related symptoms on exposure to heavy traffic (2002);
- Investigation of possible risk of congenital anomalies in the vicinity of the Maghtab Landfill and the Marsa Power Station (2002);
- Investigation of possible higher cancer rates around the Maghtab Landfill and the Marsa Power Station (2005).

Asthma is considered as a disease resulting from complex interactions between genetic and environmental factors. Since asthma-related morbidity and mortality have risen constantly over the past decades, many studies were conducted to identify and evaluate the factors responsible for the onset and/or aggravation of the underlying inflammation. Various atmospheric toxic compounds appear to be responsible, and some experts think that asthmatics are excellent indicators for atmospheric pollution and its intensity.

The International Study of Asthma & other Allergies in Childhood [I.S.A.A.C.]

The International Study of Asthma & other Allergies in Childhood [I.S.A.A.C.] was done in **153 centres in 56 countries in 6 regions using standardised methodology**. A written questionnaire was given to parents of at least 3000 6–7 yr old children per centre and a written and video questionnaire was given to at least 3000 13–14 yr old children per centre. **The study was repeated after 7 years.**

Among the 6-7 year olds the results showed that:
- **diagnosed asthma increased from 7.5% in 1994 to 14.8% in 2002**;
- If trucks pass almost all the time through child's road then s/he was **more likely to have a nocturnal cough** in the absence of a chest infection in 2001;
- **diagnosed rhinitis increased from 14.7% in 1994 to 22.2% in 2001**;
- **diagnosed eczema increased from 4.4% in 1994 to 11.2% in 2001**;
- The geographical distribution of wheezing, rhinitis and eczema showed an **increased prevalence in the Great Harbour, south-eastern and southern parts of Malta**.

Among the 13-14 year olds the results showed that:
- **diagnosed asthma increased from 11.1% in 1995 to 14.1% in 2002**;

- If trucks pass almost all the time through child's road then s/he was **more likely to have wheezed sometime in his life and suffer from a nocturnal cough** in the absence of a chest infection in 2002;
- **diagnosed rhinitis increased from 32.2% in 1994 to 40.7% in 2002**;
- **diagnosed eczema increased from 8.8% in 1994 to 11.5% in 2002**;
- The geographical distribution of wheezing, rhinitis and eczema showed an **increased prevalence in the outer harbour, inner harbour, south-eastern and southern parts of Malta**.

The European Community Respiratory Health Survey (ECRHS)

The European Community Respiratory Health Survey (ECRHS) was held in **an urban (Fgura) and a suburban area (Zejtun)** of the island of Malta in 2001.

The first part of the study aimed to investigate the prevalence of asthma-related and allergic rhinitis-related symptoms and to compare the results in respect to their urban and suburban location along a south-east direction from the Marsa Power Station and with Fgura, the urban location, being traversed by a major artery of traffic.
The ECRHS questionaire used in other studies, and with further questions added, was sent to one-third of the population of Fgura and Zejtun aged 20-44 years.
The results showed that:

- **One in 8 residents in Fgura and one in 10 residents in Zejtun had been diagnosed with asthma** by their doctor;
- **One in 4 residents in Fgura and one in 5 residents in Zejtun had asthma-like symptoms** without their knowledge;
- **One in 2 residents in Fgura and one in 3 residents in Zejtun had symptoms of nasal allergy**.

The second part of the study aimed to establish if there was any variation in the prevalence of asthma symptoms within the urban area itself in the relation to the traffic artery.
The Urban area was divided into four equal rectangular areas 250m wide, A, B, C and D. Area B carried the area with the traffic artery, A was upwind from area B while C, D were downwind. The suburban area was labeled Z.
The results concluded that:

- **living close to a main traffic artery increases the risk of asthma-related symptoms.** Area D which is 250-500 m away from the main traffic artery showed lower levels of asthma-related symptoms when comparable to 3 areas within 250m of the main traffic artery. Prevalence of symptoms is area D was comparable to lower traffic suburban area Z.
- **The levels of nasal allergy symptoms were similar across the urban area.** Area D showed the levels of allergic rhinitis similar to the urban areas A, B and C but lower than suburban area Z.

Investigation of possible risk of congenital anomalies in the vicinity of the Maghtab Landfill and the Marsa Power Station

A descriptive study looking at how adjusted congenital anomaly rates vary with distance from the Marsa Power Station was done in 2002.

The results showed that:

- **there was no association between the Marsa power source and the prevalence of congenital anomalies.** There was a slightly higher proportion of babies with multiple anomalies involving 2 or more systems in the 1km zone and the 2km zone as compared to the proportion for the other zones but the differences were not statistically significant.
- **there was no particular trend for the distribution of congenital anomalies for zones at increasing distance from Marsa Power Station.** Prevalence rates for congenital anomalies ranged from 3.1 to 5.5 per 100 births throughout the zones.
- **However, it did show a higher frequency of foetal deaths among babies with anomalies in the first zone (1 km) and the second zone (2 km), around the Marsa plant.** In these two zones the **proportions of foetal deaths were 8.8% for the first zone (1 km) and 8.1% for the second zone (2 km),** while the proportions of foetal deaths among babies with anomalies for the other zones was 2.4%.

Investigation of possible higher cancer rates around the Maghtab Landfill and the Marsa Power Station

A descriptive study looking at how adjusted cancer rates vary with distance from the Marsa Power Station was done in 2005.

The results show:

- **a statistically significant change in the rate of cancer of the lungs with increasing distance from the Marsa power station.**
- No association between the other specific cancer rates and distance from the power station was found.
- **The relative risk is greatest at the point source (RR: 1.15)** and **remained significantly raised for a distance of 2 km from the Marsa Power Station.**

Public Health Benefits of Improved Air Quality

Concerted policies implemented in **Switzerland and neighbouring countries in the 1990s** resulted in a decrease in air pollution and a range of health improvements.

- repeated cross-sectional investigations in school classes observed a **decrease in irritative symptoms and respiratory disease in children**. This change was correlated with **a decline in PM levels**.
- The Swiss cohort study SAPALDIA followed lung function decline among adults during the same time span. Age-related lung function decline was associated with air quality: in particular, the **11-year decrease in individually estimated home outdoor PM_{10} levels was associated with attenuated decline in lung function**.
- Air-quality improvements had a beneficial effect on respiratory symptoms: a mean **decline of PM_{10} of 6ug/m3 coincided with 259 fewer people with regular cough, 179 fewer people with chronic cough or phlegm and 137 fewer people with wheezing and breathlessness per 10,000 adults.** Additionally, the change in pollution was associated with a decline in new onset of asthma in adults, indicated by chronic cough.

Studies conducted **before and after the Olympic Games** provide an opportunity to assess the public health benefits of air pollution reduction in a city.

- in **1996, Atlanta, USA**, implemented several drastic measures to reduce pollution. During the 3 weeks of the games ozone peak-hour levels fell 28%, NO_2 peak-hour levels fell 7%, carbon monoxide 8-hour levels fell 19% and PM_{10} daily mean fell 16% compared with the 3-week periods before and after the games. The results in health impact were a **>40% reduction of consultations in medical practices for asthma in children, and a decline of 11-19% of asthma-related visits to emergency departments.** Over the same period, children's medical visits for other reasons barely changed.
- In **2008, for the summer Olympic Games in Beijing, China, mean $PM_{2.5}$ and PM_{10} concentrations were lower by 31% and 35%, respectively**, during the Olympic period compared with the non-Olympic period. Several studies are underway to examine the association between air pollution and subclinical health outcomes before, during and after the 2008 games.

Benefit of Clean Air Policies

While the relative risks associated with current levels of ambient air pollution are usually quite small, the overall impact of air pollution on public health is substantial, and thus the benefit of clean air policies can be very large.
Air Pollution and Health: a European Information System (APHEIS) was created in 1999 to provide policy- and decision-makers, environmental and health professional, the general public and the media with resources on air pollution. A recent evaluation of APHEIS, APHEIS-3, covered 23 cities with a total population of almost 39 million people. It estimated that:

- **11,000 premature deaths** could be prevented annually if long-term exposure to **$PM_{2.5}$ were reduced to 20ug/m^3**.
- The **mean life expectancy of a 30-year-old person** could be prolonged, depending on the geographical area, by **2-13 months if $PM_{2.5}$ concentrations were restricted to <15 ug/m^3**.

The project provided evidence that the current air-quality standards legislated by the European Union were insufficiently stringent to protect a large part of the European population.
In **APHEIS: Health Impact Assessment of Air Pollution Communication Strategy** the 26 European cities had an annual mean level of **PM_{10} of 54ug/m^3** with an exposed population of about 41.5 million. It is estimated that **reducing the annual level to 40 ug/m3 means a beneficial reduction of 8,550 deaths** due to long-term exposure.
In a study of the health benefits attributed to air pollution reduction in **Austria, France and Switzerland**, with an exposed population of around 80 million people and an annual **mean PM10 level of 21 ug/m^3**, it was estimated that **reducing the PM_{10} level to 7.5ug/ m^3 would mean 40,600 less deaths, 18,508 less hospital admissions for respiratory causes, 29,500 less hospital admissions for cardiovascular causes and 47,100 less cases of chronic bronchitis in adults**.
In a health impact assessment of **13 cities in Italy**, with an exposed population of around 10 million people and an **annual mean PM_{10} level of 45 ug/m^3**, it was estimated that **reducing the annual level to 40 ug/m^3 would mean 2,270 less deaths, 225 less hospital admissions for respiratory causes, 176 less hospital admissions for cardiovascular causes and 1,114 less cases of chronic bronchitis in adults**.
In a health impact assessment of the **Barcelona metropolitan area in Spain**, with an exposed population of around 3.9 million people and an **annual mean PM_{10} level of 50 ug/m^3**, it was estimated that **reducing the annual level to 40 ug/m^3 would mean 1,200 less deaths, 390 less hospital admissions for respiratory causes, 210 less hospital admissions for cardiovascular causes and 1,900 less cases of chronic bronchitis in adults**.
Another health impact assessment in Spain (the entire Iberian Peninsula, the Balearic Islands, Ceuta and Melilla) estimated that **1,720 all-cause deaths (6 per 100,000 population) in the over-30 age group** and **1,450 all-cause deaths (5 per 100,000 population) in the 25-74 age group** could be prevented annually if **an average annual reduction of 0.7 µg/m^3 in $PM_{2.5}$ levels** were achieved,

Air-Quality Regulation Framework in Europe

Air-quality regulation in Europe is currently legislated by the existing EU air-quality policy framework. This legislation has established health-based standards and objectives for a number of air pollutants. **Specifically, council Directive 1999/30/EC relates to limit values for SO_2, NO_2 and NO_x, PM_{10} and lead in ambient air.**

In 2008, the EU adopted a **new air-quality directive**, the Directive on Ambient Air Quality and Cleaner Air for Europe (Directive 2008/50/EC). **It is the first EU directive to include limits on ambient concentrations of $PM_{2.5}$. In addition, it requires reducing exposure to $PM_{2.5}$ in urban areas by an average of 20% by 2020 based on 2010 levels.**

Although the new air-quality directive is a step forward towards reducing air pollution in Europe, the **current scientific evidence calls for much more stringent standards**. **The new directive does not follow the guidelines developed by the World Health Organisation in 2005.**

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