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Health Effects of Outdoor Air Pollution in Copenhagen

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Introduction

We breathe in, on average, 10,000 l of air every day, and hereby, a mix of polluting substances present in the air, originating from traffic emissions, woodburning for heating, and industrial and agricultural activities. These substances, notably particulate matter and gases, remain in the atmosphere as a dirty umbrella over cities and large urbanized areas. Breathing air contaminated with toxic substances entails health risks for individuals and entire populations, posing huge public health challenges. Policy measures initiated during the 1960s and 1970s in the USA and Europe were able to drastically reduce the air-polluting activities and emissions of the past, including in Denmark, where, since the 1990s, we have had constant improvements in air quality. This has led to the perception that the air pollution levels we observe today in Denmark are not hazardous to our health. However, research since the early 1990s, including substantial evidence from Denmark, has clearly indicated that health effects still exist even at low air pollution levels, way below EU air pollution limit levels. Stricter ambient air quality standards have thus been advocated by the World Health Organization [1], which, in its latest report, recommends that levels of fine particulate matter $PM_{2.5}$ should not exceed 5 $\mu g/m^3$, and NO_2, not 10 $\mu g/m^3$. These new, significantly reduced guidelines have guided the revision of the EU Ambient Air Quality Directive, which was adopted in Fall 2024, setting new limit values for $PM_{2.5}$ and NO_2 to 10 and 20 $\mu g/m^3$, respectively, a significant reduction from 25 and 40 $\mu g/m^3$ that are still valid, as set in 2008. While Denmark complies with a European current limit value for $PM_{2.5}$ of 25 $\mu g/m^3$ and is close to achieving compliance with a new limit value of 10 $\mu g/m^3$, we are still all exposed to $PM_{2.5}$ above 5 $\mu g/m^3$, and thus, we all continue to breathe air that is harmful to our health.

There is now established evidence that exposure to air pollution increases the risk of a number of major chronic and infectious diseases, including asthma in children and adults, autism spectrum disorder in children, acute lower respiratory infections (ALRI) in children and adults, chronic obstructive respiratory disease (COPD), myocardial infarction, stroke, atrial fibrillation, heart failure, lung cancer, type 2 diabetes, and dementia, and leads to premature mortality. Air pollution in pregnancy leads to lower birth weight in newborns, infant mortality, as well as increased risk of gestational hypertension and preeclampsia in mothers. Most of these health effects have also been documented in Denmark, where current annual mean levels of $PM_{2.5}$ are around 10 $\mu g/m^3$. Danish studies have also produced convincing evidence that adverse health effects exist even below $PM_{2.5}$ levels of 10 $\mu g/m^3$, and that there is no evidence of a safe lower limit. It is important to note that the overall burden of air pollution is not yet fully elucidated, and current research is rapidly pushing forward to identify new links between air pollution and 'new' diseases, including COVID-19, cancer other than lung, including breast, liver, colon, bladder, brain, and stomach cancer, Parkinson's Diseases, multiple sclerosis, psychological disorders (depression, anxiety, suicide), type-1-diabetes, childhood cancer, attention deficit and hyperactivity disorder (ADHD), neurodevelopment in children, gestational diabetes, infertility, birth outcomes (congenital anomalies, preterm birth, stillbirth) among others. This report provides a short narrative overview of the main health effects related to air pollution, relevant mechanisms, and an overview of the epidemiological studies on air pollution health effects and major findings in Denmark.

Main Conclusion and Advice

Air pollution is a ubiquitous environmental exposure with a number of well-documented adverse health effects, including increased risk of chronic respiratory diseases, asthma and COPD, cardiovascular disease, stroke, ALRI, type 2 diabetes, lung cancer, dementia, and premature mortality. In children, air pollution increases the risk of asthma, ALRI, and autism spectrum disorder. Prenatal exposure to air pollution increases the risk of low birth weight in newborns and the risk of preeclampsia and gestational hypertension in pregnant women. Findings from studies on the health effects of air pollution in Denmark agree well with the international literature despite relatively low air pollution levels in Denmark. It has been estimated that around 3,500 deaths per year are attributable to air pollution in Denmark in 2022. There is sufficient evidence to claim that any reduction in air pollution would bring substantial health benefits. Certain populations, including children, pregnant women, elderly citizens, persons with chronic diseases, those in the lowest socio-economic groups, and people exposed to high levels of air pollution (people who are physically active in cities, working close to pollution sources, etc.) are more susceptible to the adverse health effects of air pollution, and additional measures are needed to protect these groups. Unequal distribution of the health risks associated with differential exposure to poor air quality between people in different subpopulations violates the basic principle of environmental equity.

Air Pollution: short- and long-term health effects

Ambient air pollution is ubiquitous exposure that affects everybody to some extent and, thus, the most studied environmental exposure. Air pollution contains a mix of gases and particles, which, via inflammation and oxidative stress, are the main mechanisms that affect a number of organs in the human body, increase the risk of a number of health outcomes, and lead to premature mortality. Thus, air pollution is one of the major environmental stressors and the most studied environmental pollutant. Air pollution is a complex mixture including particulate matter with a diameter <10µm (PM_{10}), <2.5µm ($PM_{2.5}$), <0.1µm (ultrafine particles; UFPs), and gases: nitrogen dioxide (NO_2), nitrogen oxide (NO_x), sulphur dioxide (SO_2), carbon monoxide (CO), ozone (O_3), and black carbon (BC), among many others. Air pollution epidemiology is concerned with the health effects related to exposure to air pollution, and it is typically divided into two large areas: 1) short-term studies - studies of health effects related to acute or short-term exposures to air pollution, lasting over several hours, days or weeks, and 2) long-term studies - studies of health effects of chronic or long-term exposures to air pollution, lasting several months, years, decades, or an entire lifetime. Short-term studies provide an answer to the question of whether short-term exposure to high levels of air pollution (day with high levels of air pollution, several hours of exposure in heavy traffic, etc.) can trigger adverse effects, such as exacerbation of an existing disease etc. Typical health effects resulting from short-term or acute exposure to air pollution include cough, headache, irritation of the eyes, nose, and throat, allergic reactions, asthma symptom aggravation, asthma medication use, wheezing, complication of symptoms in elderly subjects with chronic respiratory and cardiovascular disease, possibly leading to hospitalization or even death. Long-term air pollution studies give an answer to the question of whether, every day, low air pollution concentrations lead to adverse health effects when accumulated over long periods of time. Health effects resulting from long-term or chronic exposure to air pollution are chronic diseases, such as asthma in children, the incidence of chronic obstructive pulmonary disease (COPD), asthma, cardiovascular disease, stroke, diabetes, lung cancer, breast cancer, pneumonia, or death in adults. It is important to note that short-term studies establish whether a pollutant is a trigger of a health effect, while long-term studies are used to establish causal relationships between air pollutants and a specific health outcome and are used in the evaluation of air pollution as a risk factor for a disease.

Global burden of disease due to air pollution

The latest Global Burden of Diseases (GDB) Study estimated that 8.1 million premature deaths worldwide were attributed to ambient and household $PM_{2.5}$ in 2021, making it the second highest-ranking risk factor for death after high blood pressure and above tobacco and dietary risks. [2,3] This GDB approach includes mortality from seven causes of death that have been causally linked to air pollution: ischemic heart disease (IHD), cerebrovascular disease, chronic obstructive pulmonary disease (COPD), type 2 diabetes, lower respiratory infections (LRI), lung cancer and mortality in children under 5 years.[2,3] Most of the deaths and DALYs (ca. 60%) attributable to $PM_{2.5}$ were due to ischemic heart and cerebrovascular diseases, followed by COPD, ALRI, and lung cancer. Ambient $PM_{2.5}$ contributed globally to 20% of deaths from ischemic heart disease, 26% of cerebrovascular disease, 40% of COPD, 30% of lower respiratory infections, 19% of all lung cancer, 19% of diabetes, and 31% of deaths in babies less than 28 days old.[3,4] It is important to note that even in areas with low and decreasing air pollution levels, as in Denmark, mortality due to ambient $PM_{2.5}$ may increase due to growing certainty of the evidence for the inclusion of new health outcomes in the health risk assessment, stronger associations between PM2.5 and health found in newest studies, as well as rapidly aging populations.

In Denmark, the latest estimate of the annual number of premature deaths due to air pollution for the 3-year average for years 2020-2022 is 3,550 deaths (3,440 due to $PM_{2.5}$, 4 due to NO_2, 90 from ozone, and 18 due to SO_2).[5] It has been estimated for Copenhagen municipality in 2022 that approximately 415 premature deaths are attributable to ambient air pollution, mostly due to long-term exposure.[6]

How do we get sick from air pollution?

We are mainly exposed to air pollution via inhalation, where pollutants get to our lungs and bloodstream. Another exposure to air pollutants comes via ingestion and uptake of pollutants through the skin. Direct exposure to air pollution in the brain comes through the nose and the transfer of fine particles and gasses via the olfactory membrane. Transplacental exposure to air pollution during pregnancy is the main exposure to unborn children. The central biological mechanisms of air pollution that damage the lung, heart, and blood vessels is inflammation,[7,8] which is also believed to be involved in endothelial dysfunction, prothrombotic changes, hypertension, and altered heart rate variability, relevant for cardiovascular diseases; the promotion of insulin resistance and type 2 diabetes (systemic inflammation, inflammation in fat tissue); and neuroinflammation in the brain which is relevant for changes in the brain relevant for neurodegenerative and psychiatric diseases. Air pollution exposure during pregnancy can cause adverse effects in the placenta, the mother (risk of hypertensive disorders, gestational diabetes), and the baby in terms of decreased birth weight, premature birth, etc. Air pollution exposure may affect reproductive health in both men (sperm quality) and women (ability to get pregnant). Air pollution impacts a number of diseases, as shown in Figures 1-3.

Air Pollution and adult diseases

Air pollution has been linked to a number of adverse health outcomes in adults, as illustrated in Figure 1.

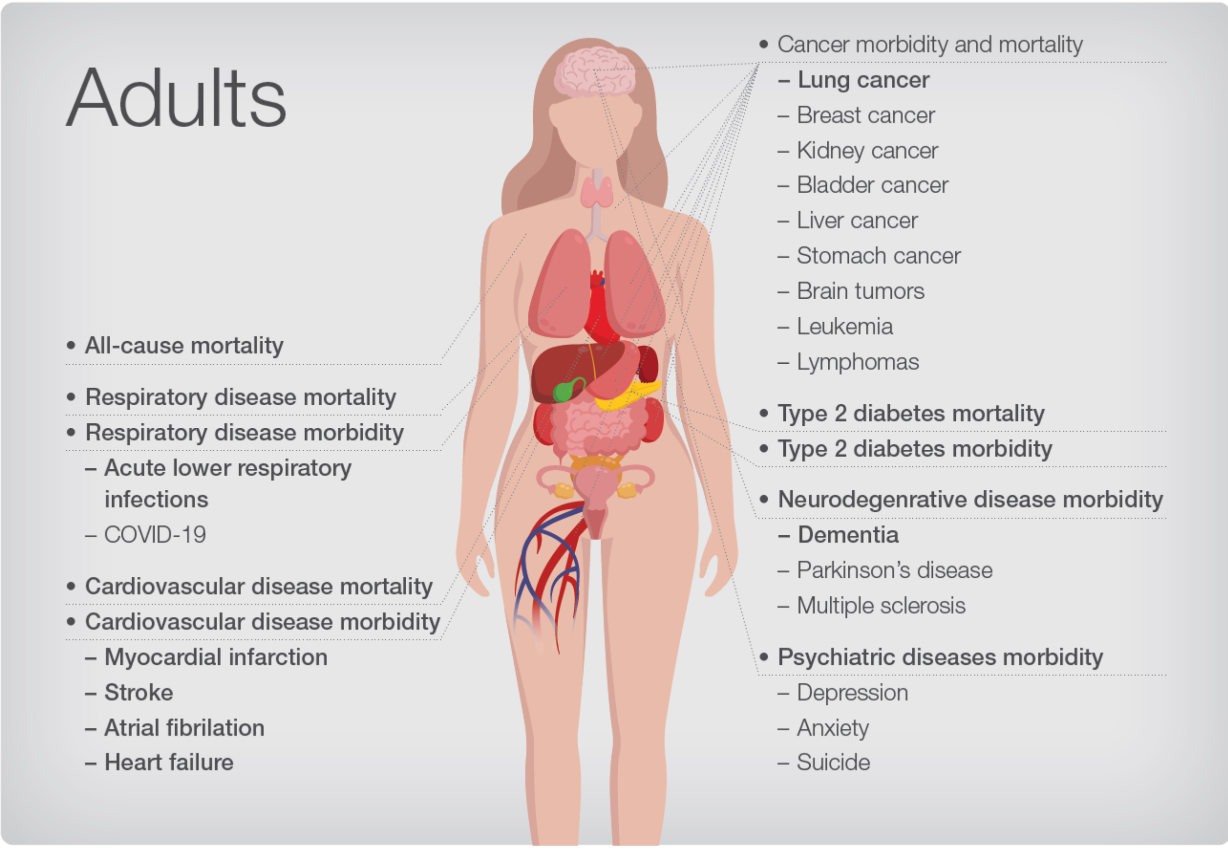

Figure 1: Adult disease outcomes for which evidence is sufficient to establish a causal association with air pollution are listed in bold, while outcomes that are currently being studied but the evidence is still not sufficient to establish whether the association is causal are listed in regular, non-bold text.

Mortality

Mortality is one of the most studied outcomes and carries the most weight in the evaluation of the evidence on health effects related to air pollution, which is used in GBD estimation. If lifelong exposure to air pollution contributes to an increased risk of a number of chronic and infectious diseases from childhood throughout a lifetime, then the ultimate consequence is that air pollution exposure shortens one's life, leading to premature death. Notably, infant mortality has been one of the first indications of the harmful effects of exposure to high levels of air pollution described in the London Fog episode but is described later in the section on childhood outcomes.

The association between $PM_{2.5}$ and all-cause mortality is well established, and the strength of the association has been increasing with the addition of new studies to the evidence base. Meta-analyses of studies on long-term exposure to air pollution and mortality by Hoek et al. from 2013 found a 6% (95% confidence interval (CI): 4-8%) excess risk in all-cause mortality per 10 $\mu g/m^3$ increase in $PM_{2.5}$,[9] which has increased to 8% in meta-analyses from 2020 by Chen and Hoek[10], and to 10% in the latest meta-analyses from 2024 by Orellano et al.[11]. This trend may be explained by several plausible reasons, including 1) improvements in exposure assessment to air pollution and better resolution of air quality data that allow for better capturing of exposure contrasts, 2) better adjustment for socio-economic status, allowing for more accurate identification of vulnerable populations who are more likely to be exposed to higher levels of air pollution and also observe stronger associations with health outcomes,[12] 3) changes in $PM_{2.5}$ mixture over time, 4) more recent studies being conducted in settings where air pollution levels have gone down, which paired with a suspected supra-linear ERF (exposure-response function) curve results in a larger relative effect per additional exposure unit at low pollutant concentrations compared to higher concentrations.[13]

Epidemiological studies on $PM_{2.5}$ and mortality have only been possible since 2020, when Danish exposure models for PM concentrations were made available. The first Danish study on $PM_{2.5}$ and mortality from 2019 showed a very strong association of a 28% increase in the risk of premature mortality per 10 $\mu g/m^3$ increase in $PM_{2.5}$, based on the Danish Diet, Cancer and Health (DCH) cohort (n=45,564)[14], much stronger than that reported in global meta-analyses[10,11]. This strong association with $PM_{2.5}$ was later confirmed in three other Danish studies: 1) 14% in the Danish Nurse Cohort (n= 24,541)[15], which utilized Danish DEHM/UBM/GiS air pollution prediction model with high 1x1 m resolution (same as used in Hvidtfeldt, Severi [16]); 2) 8% in a nationwide case-control study using the Danish DEHM/UBM model for air pollution estimates with 1x1 km^2 resolution[17], and 3) 23% in a prospective cohort of adults aged 30 years and older in year 2000 (n= 3,083,227), using air pollution estimates developed for the ELAPSE project with a 100x100m^2 resolution.[18] Results for NO_2 from these four studies show more consistent associations with those reported outside Denmark, with RR ranging from 0.95 to 1.07, in line with those reported in international literature.[19]

Morbidity

In this review, we focus on the morbidity (incidence of disease) outcomes selected by the recent WHO (Estimation of morbidity from air pollution and its economic costs) EMAPEC project, based on the comprehensive review of evidence (meta-analyses) on long-term exposure to air pollution and morbidity. We refer to the meta-analyses for each of the eleven outcomes identified in this project[20]. For other outcomes and for short-term exposure studies, we list the newest meta-analyses or significant papers that we have identified.

Respiratory health

The respiratory tract is the first portal of entry for air pollutants, which adversely affect the lungs before birth, in early life, and throughout the entire lifetime. Typical biological effects of air pollution include a suppressed immune system, inflammation, oxidative stress effects, increased risk of sensitization, impaired lung growth, and lung function decrements in children and adults.[8,21] There is strong evidence that long-term exposure to air pollution impairs lung function development and reduces lung function in children[22], as well as in adults[23], and leads to the development of a range of respiratory diseases, such as asthma in adults[24], COPD[25], and it increases the risk of premature death due to respiratory diseases[10]. Furthermore, air pollution presents a substantial burden in the daily life of respiratory disease patients, where exposure to short-term peaks in air pollution triggers exacerbations of the manifest disease, such as cough, shortness of breath, difficulties in breathing, asthma attacks, exacerbation of COPD, increased use of relieve medication, emergency room visits, hospitalizations, and even death. Around the world, since the pandemic in 2019, researchers have been working to understand a potential link between COVID-19 and air pollution. There is now strong evidence that both short- and long-term exposure to air pollution can contribute to an increased risk of infection with another virus in the coronavirus family, called SARS-CoV-2, which can be severe and result in premature death.[26]

Danish studies have also shown that short-term exposure to air pollution can trigger asthma hospitalizations in and adults.[27,28] Additionally, Danish studies have shown that long-term exposure to air pollution can contribute to the development of asthma in adults[29-31], as well as COPD[32-34].

Similarly, recent Danish studies have also shown that long-term exposure to air pollution can contribute to an increased risk of contracting pneumonia[35] and premature death due to pneumonia[18], as well as increased risk of hospitalization and death from COVID-19.[36]

Cardiovascular disease

A wealth of evidence links air pollution to heightened cardiovascular morbidity and mortality. Two important review position papers on air pollution and cardiovascular disease by medical societies by the American Heart Association from 2010[7] and by the European Society of Cardiology,[37] in 2015, make a strong statement in recognizing air pollution as a risk factor for cardiovascular disease, as well as providing a nice overview of epidemiological evidence and mechanistic understanding. Several recent meta-analyses assessing the impact of short-term exposures to $PM_{2.5}$ (per 10 μg/m^3 increase during the prior few hours-to-days) have been published. In 34 studies, $PM_{2.5}$ exposure significantly increased the risk for acute myocardial infarction by 2.5%.[38] Hospitalization or death from heart failure (2.1%; 35 studies),[39] stroke (1.1%; 94 studies),[40] and arrhythmia (1.5%; 23 studies)[41] have also been shown to be increased, and similar risks were also reported for short-term exposures to NO_2. While these relative risks are modest, short-term exposures to $PM_{2.5}$ account for up to 5% (population-attributable fraction) of myocardial infarctions worldwide because hundreds of millions of people are continuously impacted.[42] Longer-term exposures over several years appear to pose amplified risks over and above the acute risks. A meta-analysis demonstrated that living within an area facing a chronic elevation in $PM_{2.5}$ leads to a 10.6% increase (per 10 μg/m^3) in cardiovascular mortality, roughly 5- to 10-fold the risks following acute exposures.[9] There is now sufficient evidence to conclude that long-term exposure to air pollution is linked to the incidence of ischemic heart diseases[43], stroke[44], and hypertension[45], as well as premature mortality from cardiovascular diseases[10]. The newest research points also to a likely link between long-term exposure to air pollution and atrial fibrillation [46] and heart failure[47].

In Denmark, it has also been shown that air pollution can contribute to the development of all major cardiovascular diseases, including myocardial infarction[48,49] [50], stroke[51-53], heart failure[54], and atrial fibrillation[55,56], as well as increased mortality due to cardiovascular diseases.[15,17,18]. A report from the Danish Heart Foundation in 2017 indicated that approximately 2,000 Danes die from cardiovascular diseases due to air pollution each year, and 1,390 are hospitalized for cardiovascular diseases each year due to air pollution in Denmark.[57]

Cancers in adults

Outdoor air pollution was, in 2013, classified as carcinogenic to humans by the International Agency on Research for Cancer (IARC).[58] This sparked interest in research on air pollution as a risk factor for a number of cancer types. There is today clear evidence of a link between long-term exposure to air pollution and incidence[59] and mortality from lung cancer[10].

A number of other cancers have been examined with respect to air pollution, but without conclusive evidence. One notable study to mention is a study by Turner et al. from 2017 based on the American Cancer Prevention Study II, which linked air pollution to mortality from all types of nonlung cancers, and found that air pollution was not associated with death from most nonlung cancers, but detected associations with kidney, bladder, and colorectal cancer death, calling for more research.[60] Besides lung cancer, a number of other cancer outcomes have been considered within the European Studies on Chronic Air Pollution Effects (ESCAPE) project and the Effects of Low-level Air Pollution: a Study in Europe (ELAPSE) projects, including breast cancer,[61,62] brain tumor,[63,64] bladder cancer,[65,66] liver cancer,[67,68] stomach cancer,[69,70] cancer of kidney and parenchyma,[71,72] and leukemia [73,74]. ESCAPE and ELAPSE studies reported suggestive evidence of an association of air pollution with breast, liver, and brain cancers, presenting mixed findings for stomach cancer and leukemia and no support for kidney or bladder cancers. In Denmark, a link has also been found between air pollution and lung cancer incidence[75] and mortality[18,76], as well as investigated associations with breast cancer, [75,77,78], brain tumors,[79-81], and other cancers,[75] though findings have been quite mixed. Research on air pollution and the development and mortality of various cancers beyond the lungs is rapidly growing, and knowledge remains limited; however, based on current evidence, a potential link cannot be ruled out.

Type 2 Diabetes

A plausible biological mechanism of air pollution promoting diabetes was provided by Sun et al.[82], showing that exposure to particulate air pollution caused increased blood glucose, inflammation in adipose tissue, and insulin resistance in high-fat-diet mice. This led to a surge in epidemiological studies since 2012, and there is now sufficient evidence to establish a causal relationship between air pollution and type 2 diabetes (T2D) incidence[83] and mortality[2]. There are two Danish studies on air pollution and type 2 diabetes incidence, one from the Danish Diet and Cancer Cohort, which detected a strong association of a 4% increase in T2D incidence per 5.6 per µg/m^3 increase in

NO_2,[84] and another from the Danish Nurse Cohort which detected an 11% increase in T2D incidence for each 3.1 µg/m^3 increase in $PM_{2.5}$.[85] Furthermore, there are several studies on air pollution and type 2 diabetes mortality.[18,86]

Neurodegenerative and Psychiatric Diseases

Long-term exposure to air pollution can have detrimental effects on the brain via inflammatory reactions (neuroinflammation) and oxidative stress in the brain's nerve cells, which can lead to neurological damage and diseases, impairing optimal cognitive development in children and promoting cognitive decline in adults.[87] There is now strong evidence that long-term exposure to air pollution can contribute to an increased risk of dementia.[88] Evidence on air pollution and Parkinson's diseases[89] and multiple sclerosis[90] is emerging but still somewhat inconsistent. In Denmark, a recent study has shown a strong association between long-term exposure to air pollution and the risk of developing dementia.[91] A Danish nationwide case-control study found a 9% increased risk of Parkinson's diseases for each 3 µg/m^3 increase in NO_2,[92] however, multiple sclerosis has still not been studied in Denmark.

Psychological Disorders

Accumulating data suggests that air pollution is associated with increased depressive and anxiety symptoms and behaviors and alterations in brain regions implicated in the risk of psychopathology.[93] Meta-analyses from 2019 found suggestive evidence in support of associations between long-term exposure to air pollution with depression and anxiety and between short-term exposure and suicide, but based on limited evidence, and called for more studies on the topic. There are no Danish studies on long-term exposure to air pollution and incidence of depression or anxiety, although a recent Danish nationwide study showed a strong association with mortality from psychiatric diseases[18] that was confirmed in larger European (ELAPSE) analyses[94].

Air Pollution and children's diseases

Children are more susceptible to the adverse effects of ambient air pollution than adults due to several factors: their lungs, brains, and immune systems are under development, and toxicants from ambient air can interfere with multiple biological processes throughout life, but the impact on health is likely to be worse when exposure occurs early in life and the expected lifespan ahead is longer;

children inhale more air per unit of body weight than adults; children are more active and spent more time outdoors, and therefore breathe in more air pollution. There is compelling evidence that exposure to ambient air pollution damages the health of children in numerous ways, as illustrated in Figure 2.

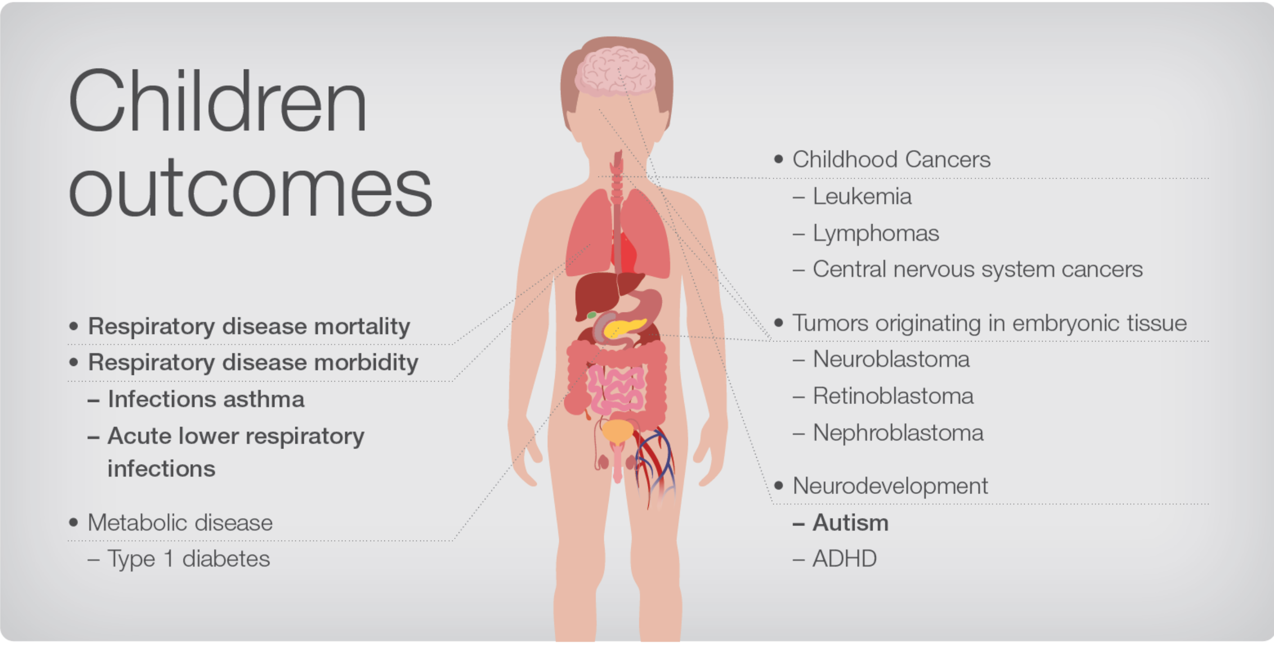

Figure 2: Air pollution has been linked to a number of adverse health outcomes in children, as illustrated in the figure above: outcomes for which evidence is sufficient to establish a causal association with air pollution are listed in bold, while outcomes that are currently being studied, but the evidence is still not sufficient to establish whether the association is causal, are listed in regular, non-bold text.

Asthma

There is strong evidence that early exposure to air pollution impairs lung function development and reduces lung function in children[22], and leads to the development of asthma in children [95]. Furthermore, air pollution presents a substantial burden in the daily life of asthmatic children where exposure to short-term peaks in air pollution triggers exacerbations of the manifest disease, such as cough, shortness of breath, difficulties in breathing, asthma attacks, emergency room visits, hospitalizations, and even death.

Danish studies have also shown that short-term exposure to air pollution can trigger wheezing in young children[96] and asthma hospitalizations in children[97]. Additionally, Danish studies have shown that long-term exposure to air pollution can contribute to the development of asthma in children[98,99].

Pneumonia

There is now sufficient evidence that long-term exposure to air pollution impairs lung function development and reduces lung function in children[22], and leads to increased risk of ALRIs in children[24], primarily pneumonia. There are no Danish studies on the long-term exposure to air pollution and ALRIs in children.

Type-1-diabetes

A few epidemiologic studies suggest that increased pre- or postnatal exposure to PM and other air pollutants is associated with an increased risk of type 1 diabetes,[189–192] but not all studies detected associations,[193] calling for more studies on the topic. A few cross-sectional studies have linked air pollution exposure with pre-clinical markers of diabetes in terms of higher fasting insulin and HOMA-IR[194–197] while findings from a study of children in Denmark do not support evidence of associations between long-term exposures to air pollution and a metabolic profile characteristic of increased risk for glucose intolerance or type 2 diabetes later in life.[198]

Childhood cancers

Acute leukemia is the most frequent childhood cancer that has been extensively studied with respect to air pollution, raising a lot of debate. At least six systematic reviews have evaluated the association of traffic-related air pollution with acute childhood leukemia,[100-105] and all but one indicated association.[103] For instance, the 2016 IARC-WHO review of air pollution noted that weak associations with childhood leukemia (especially acute lymphoblastic leukemia (ALL)) were defined as "suggestive" but "inconsistent".[105] Filippini et al., in meta-analyses from 2019, found that traffic-related air pollution was associated with excess risk of childhood leukemia, with strongest associations with acute myeloid leukemia (AML), a relatively rare type of childhood leukemia.[104] The first Danish study on air pollution and childhood cancer from 2001, in a case-control design, evaluated the contribution of NO_2 and benzene at residence to the development of leukemia, central nervous system (CNS) tumors, and leukemia.[106] In Denmark, Raaschou-Nielsen et al. found no association of NO_2 or benzene with leukemia or central nervous system (CNS) tumors but detected an association with lymphomas.[106] In a follow-up study, Raaschou-Nielsen et al. found that benzene was associated with a higher risk for childhood AML, but not ALL.[107] In summary, there is weak suggestive evidence for an association between benzene and childhood AML, calling for more data. Evidence for associations between any other air pollutant and any other type of childhood cancer is mixed and inconsistent, and thus, there is no consensus for a causal link between outdoor air pollution and childhood cancer.

Neurodevelopment

Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) are neurodevelopmental disorders associated with broad functional impairments that can substantially affect children's and families' quality of life. ASD covers a wide range of conditions, which are usually identified by the age of 5 years and are characterized by asocial behavior and difficulties in communication and language. In children, long-term exposure to air pollution has been linked to an increased risk of ASD,[108] while evidence of ADHD is emerging but still inconclusive.[108] A smaller-sized Danish study suggested that air pollutant exposure in early infancy increased the risk of autism and Asperger's,[109] and another large Danish nationwide study found an association between NO_2 in early life and ADHD.[110] A recent Danish nationwide study found that long-term exposure to air pollution in childhood contributed to poorer cognitive performance in children, in terms of lower school grades on the grade 9 exam, making a major contribution to the growing evidence base internationally in this field.[111]

Air Pollution and pregnancy and birth outcomes

Birth outcomes

A growing body of research provides evidence of an association between maternal exposure to air pollution and adverse birth outcomes, including low birth weight, preterm birth, congenital anomalies, and stillbirth. While associations with birth weight are established, evidence is still mixed for other birth outcomes, demanding more research.

Several recent meta-analyses report an increased risk of low birth weight and reduced mean birth weight associated with NO_2,[112] $PM_{2.5}$[113-115] or ozone[115]. Pedersen et al., from 2013, in a large European ESCAPE project based on 14 European cohorts, found an association of $PM_{2.5}$ during pregnancy with an increased risk of low birth weight.[116] A review suggests that pregnant women who are smoking, are underweight or overweight/obese, or have low SES are a vulnerable subpopulation when exposed to ambient air pollution, with an increased risk of having a child with low birth weight.[117] Epidemiological evidence on air pollution and preterm birth is more mixed and less convincing than that for birth weight. Some studies have found a positive association between maternal exposure to $PM_{2.5}$ and preterm birth.[118-121] On the other hand, the ESCAPE study on air pollution and preterm birth based on 13 European cohorts found no association between air pollution and preterm birth,[122] pointing out the need for more studies on the topic. Evidence on congenital anomalies is still sparse and mixed. A meta-analysis of four studies on air pollution and congenital anomalies found increased risks of coarctation of the aorta and of tetralogy of Fallot with exposure to NO_2 and SO_2, as well as PM_{10} and an increased risk of atrial septic defects.[123] Another systematic review and meta-analysis showed a significant association between exposure to NO_2 and coarctation of the aorta.[124] Stillbirth is defined as fetal death occurring at a birth weight of $\geq$ 1000 g or at $\geq$ 28 weeks of gestation. Meta-analysis from 2020 shows suggestive associations between long-term exposure to $PM_{2.5}$ and ozone and stillbirth, as well as short-term exposure to ozone with stillbirth, but also that evidence is sparse, and further studies are needed to strengthen the evidence.[125]

A Danish study found no association between air pollution and birth weight.[126] A Danish study on air pollution and congenital anomalies found suggestive evidence of a link of NO_2 with anomalies in the ear, face, and neck.[127]

Pregnancy outcomes

Air pollution may lead to complications in pregnancy (Figure 3), including gestational hypertension and preeclampsia and gestational diabetes mellitus (GDM). Meta-analyses found an association of long-term exposure to $PM_{2.5}$ with pregnancy-induced hypertensive disorders and preeclampsia.[128-131]

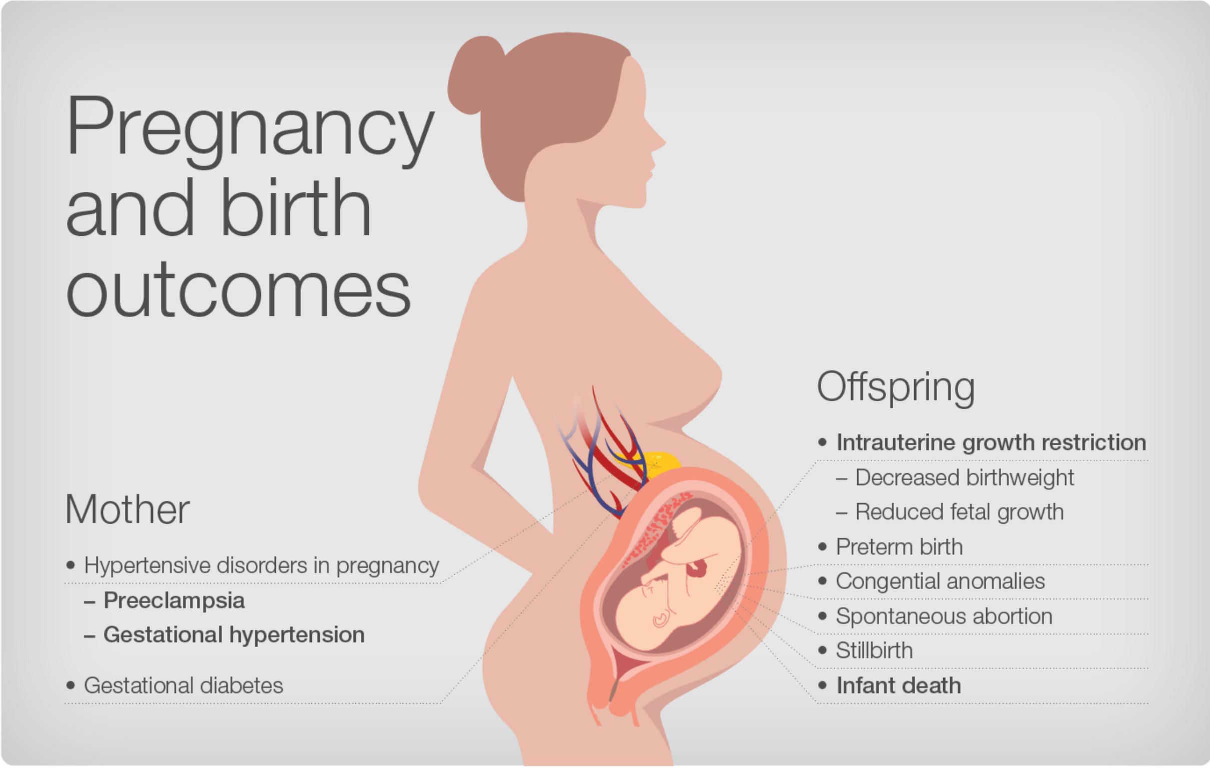

Figure 3: Air pollution has been linked to a number of adverse health outcomes in pregnant women, as illustrated in the figure above: outcomes for which evidence is sufficient to establish a causal association with air pollution are listed in bold, while outcomes that are currently being studied, but the evidence is still not sufficient to establish whether the association is causal, are listed in regular, non-bold text.

In a Danish study with 72,745 pregnancies, Pedersen et al. found an association of NO_2 in the first trimester with an increased risk of pre-eclampsia and pregnancy-induced hypertensive disorders.[132] Pedersen et al., in a study based on the Danish National Birth Cohort, investigated the link between NO_2 during pregnancy and the risk of GDM and found inconsistent associations that depended on the definition of GDM.[127] To conclude, there is evidence for an association between air pollution and hypertensive pregnancy disorders, including preeclampsia, while more studies on air pollution and GDM are needed.

Reproductive outcomes

Air pollution may influence both male and female reproductive abilities, including fecundability, fertility rate, infertility, sperm quality, etc. Both animal and human epidemiological studies support the idea that air pollutants cause defects during gametogenesis leading to a drop in reproductive capacities in exposed populations.[133] A number of experimental studies have shown that air pollution is involved in many pathologies and may act through several mechanisms that can affect reproduction: as endocrine disruptors or reactive oxygen species inducers and through the formation of DNA adducts and/or epigenetic modifications.[133] Epidemiological studies examined several different parameters of reproductive health. NO_2 levels were significantly associated with decreased fecundability in few studies,[134] and link with male infertility has been suggested but is still inconclusive.[135]

In Denmark, an association between long-term exposure to air pollution and fecundability was detected recently.[136] Another recent Danish study has found an association of air pollution with a higher risk of male infertility.[137]

Physical activity and air pollution

Physical activity reduces, whereas exposure to air pollution increases the risk of morbidity and mortality from all major cardiometabolic and respiratory diseases. Physical activity amplifies ventilation rates and respiratory uptake and deposition of air pollutants in the lungs, and it has been hypothesized that this increased exposure to air pollution during exercise outdoors may augment the harmful effects of air pollution during exercise and possibly attenuate or even reverse the benefits of exercise. Therefore, air pollution is often perceived as a barrier to exercise in urban areas, and the population is concerned about air pollution.[138-140] In many cities around the world, official air pollution alerts recommend that on days with high levels of air pollution, people should avoid going outside and being physically active to reduce their exposure to air pollution. Taking Beijing as an example, a red alert will be issued if the daily average air quality index (AQI) is forecasted to go beyond 200 and continue for more than two days[141], while other countries have lower threshold values, such as 150 of AQI in the US cities.[142] Despite sparse evidence, current research seems to show that the benefits of exercise outdoors outweigh the risks associated with enhanced uptake of pollutants during exercise.[143]

Three Danish studies, in the Danish Diet, Cancer, and Health study, with over 50,000 participants, examined whether long-term health benefits of leisure time and utilitarian physical activities (cycling, participation in sport, walking, and gardening) were moderated by exposure to air pollution. In the first paper, Andersen et al. found that the beneficial effects of participation in sports, cycling, and gardening with total, cardiovascular, and diabetes mortality were not modified/attenuated by NO_2.[144] However, they found that reductions in respiratory mortality associated with cycling and gardening were significantly higher in subjects who lived in areas with moderate/low NO_2 than in those who lived in areas with high NO_2 levels, suggesting that there might be some reduction in the beneficial effect of physical activity when exercising in areas with high air pollution, though there is still benefit. Fisher et al. found inverse associations of participation in sports and cycling with incident asthma and participation in sports, cycling, gardening, and walking with incident COPD,[145] and no interaction with NO_2, concluding that the two benefits of exercise in the prevention of chronic lung disease are not outweighed by air pollution. Similarly, Kubesch et al.[146] found inverse associations between participation in sports, cycling, gardening, and incident MI and no effect modification by NO_2. These three papers document that in urban areas with relatively low air pollution levels, such as Copenhagen, Denmark, the benefits of exercise outweigh the risks of additional exposure to air pollution during exercise. Still, it is recommended that people choose less polluted routes (parks, less busy streets) for their jogging, biking, or walking trips when possible. If it is not possible, it is still recommended to stay physically active in Copenhagen, even on busy streets, as the benefit of exercise outweighs the risk associated with additional inhalation of air pollutants during exercise.

Summary

There is very strong and sufficient evidence of the high quality of adverse health effects related to air pollution in Denmark, which is well in line with international literature. Studies from Denmark are of state-of-the-art quality and published in high-impact journals due to the unique possibilities of combining excellent, historical air pollution modeling data with Danish cohorts and high-quality health outcome data from Danish health registers. Danish studies contribute important evidence on air pollution health effects at the air pollution levels below the current EU limit value for $PM_{2.5}$ of 25 $\mu g/m^3$, and even below the new EU limit value of 10 $\mu g/m^3$, just adopted in 2024 with new revised EU Air Quality Directive. In Denmark, everyone is exposed to $PM_{2.5}$ higher than the new WHO Air Quality Guideline of 5 $\mu g/m^3$, making a strong case for stricter regulation that should work to reduce air pollution down to new Air Quality Guidelines. There is sufficient evidence to claim that any reduction in air pollution would bring substantial health benefits. Access to clean air should be a fundamental need and right for all citizens in Denmark, and European, national, and local governments have a responsibility to ensure that this fundamental right of the individual is respected and to work toward reduction in air pollution levels. To fully grasp the burden of air pollution, more research is needed on new outcomes related to air pollution, such as neurodegenerative and psychological health, rare lung and heart diseases, diseases of the eye and skin, chronic kidney diseases, cancers other than lung, adverse effects in pregnant women, birth and reproductive outcomes, and health effects in susceptible groups, including chronic cardiovascular and respiratory disease patients, children and pregnant women, and elderly. For all health outcomes, there is a need for more knowledge on relevant air pollution components and sources in order to better understand the relative contribution of different sources to health and facilitate better prevention possibilities.

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