Review Article

The Effects of Fine Dust, Ozone, and Nitrogen Dioxide on Health

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Summary

Background: Air pollutants, especially fine dust, ozone, and nitrogen dioxide, pose a danger to health worldwide. In 2005, the World Health Organization (WHO), in order to protect public health, issued global recommendations for maximum levels of fine dust (10 µg/m^3 for fine dust particles smaller than 2.5 µm [$PM_{2.5}$]), ozone, and nitrogen dioxide. The recommended levels are regularly exceeded in many places in Germany.

Methods: This review is based on relevant publications retrieved by a selective search in PubMed and, in part, on an expert statement issued in the name of the International Society for Environmental Epidemiology (ISEE) and the European Respiratory Society (ERS).

Results: Air pollutants affect the entire body, from the beginning of intrauterine development all the way to the end of life, causing premature death mainly through lung and heart disease. An epidemiological study has shown, for example, that mortality rises approximately 7% for every incremental long-term exposure to 5 µg/m^3 $PM_{2.5}$ (95% confidence interval: [2; 13]). Aside from lung and heart disease, the carcinogenic effect of fine dust is now well established. High fine-dust exposure has also been linked to metabolic diseases. For example, in a meta-analysis of cohort studies, the incidence of type 2 diabetes mellitus was found to be associated with elevated fine dust concentrations, with a 25% relative risk increase [10; 43] for every 10 µg/m^3 of $PM_{2.5}$. More recent studies have shown that these substances cause harm even in concentrations that are below the recommended limits.

Conclusion: It is very important for public health that the current EU standards for fine dust particles smaller than <2.5 µg are markedly lowered so that health risks can be further reduced, in accordance with the recommendations of the WHO.

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All across the world, the air contains contaminants from a host of sources. These substances form a mixture of many different individual components, some of them toxic. In recent decades, scientific research in this area has concentrated on the health effects of emissions from incomplete combustion processes. The most thoroughly investigated airborne contaminants, both in human exposure studies and in toxicological experiments, include fine dust, ozone, and nitrogen dioxide. Because these irritant or harmful substances are technically relatively easy to quantify, their levels have been measured widely in a large number of countries during the past several decades.

This article is based on a selective search of the literature in PubMed and, in part, on an expert report prepared on behalf of the International Society for Environmental Epidemiology (ISEE) and the European Respiratory Society (ERS) (e1).

Experiments on cells, animals, and humans

Toxicology studies and controlled exposure of volunteers serve to examine health effects resulting from chemical and physical properties of harmful substances in the air. These investigations provide important data on biological effects in the human body, but do not permit conclusions as to the incidence of diseases or the worsening of existing illness. Controlled exposure studies on human volunteers are particularly useful for determining short-term changes, e.g., in lung function or markers of inflammation. Even these investigations are, on ethical grounds, usually conducted only in relatively healthy persons *(eBox 1)*.

Risk factor research in humans: analytical epidemiology

On grounds of ethics and practicality, the incidence of illness and death cannot be investigated in randomized clinical trials. This principle applies to air pollution just as it does to other risk factors, e.g., smoking. The method of choice for estimating the short- and long-term effects in different age groups and patient cohorts is therefore the large epidemiological observational study. Air pollution studies use the same tried and tested methods by means of which the deleterious effects of other generally accepted risk factors such as hypertension, hypercholesterolemia, and smoking (active and passive) were established. Because population exposure is meanwhile well documented by

TABLE

Associations regarded as scientifically confirmed on the basis of expert evaluation up to 2016*

Airborne contaminant	Health effects	Assessment	Source
Fine dust ($PM_{2.5}$)	Mortality	Causal	(e2)
	Cardiovascular disease	Causal	(e2)
	Cancer disease	Causal	(e5)
	Airway disease	Probably causal	(e2)
Ozone	Short-term effect on airway disease	Causal	(e9)
	Short-term effect on cardiovascular disease	Probably causal	(e9)
	Airway disease	Probably causal	(e9)
Nitrogen dioxide	Short-term effect on airway disease	Causal	(e10)
	Airway disease	Probably causal	(e10)

* The causality criteria for (e5) are described in (e11, e12) and those for (e2, e9, e10) in (e13).

widespread and continuous measurement of airborne contaminants in many different countries, scientists can now gauge the short- and long-term effects of these substances under real world conditions in broad-based population studies.

Investigation of short-term effects

Epidemiological research began with time-series studies of specific morbidity or mortality based on death registers or hospital admission data (16). These studies are methodologically very robust, because they use high-quality population-wide data and are affected only slightly or not at all by self-selection, measurement errors, or certain confounders: every death is counted, no-one can decline to participate in the study, and air pollution is measured with sensitive, standardized instruments in population centers. Daily changes in the levels of contaminants are compared with daily rates of death or hospital admission for asthma, bronchitis, myocardial infarction, or stroke and the short-term effects of higher exposure to dust, nitrogen oxides, or ozone are calculated. The analyses take other risk factors into account that vary in the short term, such as temperature or the influenza season. Long-term risk factors (smoking or dietary habits, lifestyle, occupational exposures, or exposures from indoor sources) do not need to be considered in such studies, because they are not associated with short-term fluctuations in airborne contaminants, so there can be no confounding of effects. The same applies to panel studies, in which probands are investigated several times at intervals of days or weeks. Here, the change in air pollution before the study visits is associated with alterations in various physiological parameters (lung function, inflammation markers, blood pressure, and others), although owing to the study design only risk factors that are variable in the short term (e.g., passive smoking on the evening before examination) have to be considered as possible confounders.

Investigation of long-term effects

In order to determine the longer-term health effects of chronic exposure to airborne contaminants, very large cohort studies have been carried out particularly in North America, Europe, and, in recent years, countries such as China (17–20). These studies are scientifically complex, costly, and of high validity. As a rule they use cohorts originally recruited for research targeting common illnesses such as cancer or cardiovascular disease (ACS Cancer Prevention Study, KORA Study, Heinz Nixdorf Recall Study, etc.). These studies are characterized by detailed and high quality data, including the careful documentation of many personal risk factors and medical history data as well potential confounders—for which adjustments can be made in the course of analysis (for indoor air exposure as a potential confounder, see *eBox 2*). They include children and both healthy and sick persons, and permit documentation of sensitive biomarkers and long-term exposures.

One challenge in the planning, conduct, and analysis of long- and short-term epidemiological studies is that fine dust, ozone, and nitrogen dioxide have common sources and thus often occur at the same time in the same place, affecting the human body jointly (23). Furthermore, other harmful airborne substances, such as soot, ultrafine particles (<100 nm), or volatile organic compounds, may be present in addition to fine dust and nitrogen dioxide (24). For this reason, additional measurements, satellite data, and complex modeling are used to estimate the exposure, ideally in terms of both time and space. The closer the correlation between the individual airborne contaminants, the more difficult (or even impossible) it is to isolate their respective effects. Although the sources of the substances overlap, their distribution in the ambient air may well differ. For example, fine dust is relatively evenly distributed: the difference in concentration between the districts of a city with the highest and lowest exposure is in the range of 2 to

4 µg/m^3. For NO_2, in contrast, the difference is much greater, sometimes more than 20 µg/m^3 (25). This results in a less than perfect correlation of exposures, permitting partial isolation of the effects. Multicenter cohort studies with greatly different compositions (mixtures) and concentrations of contaminants enable separation of the effects of different substances.

Natural experiments and intervention studies

A particularly important contribution to causal inference has been made by quasi-experimental studies. Such "natural experiments" have resulted in dramatic reductions in air pollution levels due to environmental regulations invoked for the Olympic Games in Atlanta (26) and in Beijing (27, e14, e15) and they have shown a direct connection between temporary or permanent closure of heavily polluting industrial plants or power stations and reduction of airway diseases (including asthma). The temporary closure of a steel-mill in Utah that caused high local contamination from particulates was associated with a simultaneous two- to threefold decrease in admission of children to the hospital because of asthma and bronchitis (28). Similarly, data analyzed using sophisticated methodology show that retirements of coal and oil power plants in California were associated with a reduction in preterm births from 7.0% to 5.1% within a radius of 5 km (29). Particularly revealing is another Californian study that monitored children's lung function from 10 to 18 years of age. The authors found not only that lung function and lung growth were impaired with higher exposure, but also that a move to an area with better or worse air quality was followed by improvement or deterioration of lung development, respectively (30, e16). For example, the forced expiratory volume in 1 s (FEV_1; observed FEV_1 <80% of expected FEV_1) of 18-year-olds in regions with elevated fine-dust pollution was lower (7.9% versus 1.6% showed impairment, P = 0.002).

The *Table* summarizes the associations considered by experts to be scientifically confirmed, as of 2016 *(Table)*.

The *Box* lists the effects of harmful airborne substances on the human body that have been observed in population studies. The findings range all the way from effects in the womb through acute and chronic illness in children and adults to premature death, and many different organs and physiological processes are affected. Thousands of earlier studies (32), including the earliest on overall mortality (e17–e20) and airway disease (e3, e21) as well as prominent studies on cardiovascular disease (e4, e6), have been joined by more recent studies on metabolic diseases (diabetes: risk raised by 25% per 10 µg/m^3 $PM_{2.5}$, 95% confidence interval [10; 43] [e22]), problems during pregnancy (e.g., high blood pressure [e23] or an increase of 13% [3; 24] in preterm births per 10 µg/m^3 $PM_{2.5}$ [e24]), effects on lung and brain development in children (systematic reviews [e25, e26]), and even on

BOX

Effects of harmful airborne substances on the human body documented in population studies*

- **Airway**
  - Mortality due to airway disease
  - Morbidity due to airway disease
  - Lung cancer
  - Airway symptoms
  - Inflammation of the airway
  - Reduced lung function
  - Reduced lung growth
- **Pancreas**
  - Insulin resistance
  - Diabetes mellitus type 2
  - Diabetes mellitus type 1
  - Bone metabolism
- **Blood/circulation**
  - Hypertension
  - Endothelial dysfunction
  - Increased coagulation
  - Systemic inflammation
  - Venous thrombosis
- **Brain**
  - Stroke
  - Mental illness
  - Brain development in childhood
  - Neurodegenerative diseases
- **Heart**
  - Mortality due to cardiovascular disease
  - Morbidity due to cardiovascular disease
  - Myocardial infarction
  - Cardiac arrhythmia
  - Heart failure
  - Disorders of heart rate variability
  - ST-segment depression
- **Skin**
  - Skin aging
- **Embryo/reproduction**
  - Preterm birth
  - Reduced birth weight
  - Reduced fetal growth
  - Pre-eclampsia
  - Reduced sperm quality

*Modified from (31)

skin aging (e27). In recent years the aging brain has also been investigated as a possible site of damage by airborne contaminants, and an elevated risk of stroke (e28) and higher levels of neurodegeneration (e29), cognitive impairment (systematic review [e30]), and dementia (systematic review [e31]) have been documented in persons exposed to higher concentrations in population studies.

These effects are relatively small in size compared with those of other risk factors, e.g., smoking, but given the ubiquity of exposure they are relevant for the overall disease burden in the population. For example, epidemiological studies show an increase of around 7% [2; 13] in mortality for every 5 µg/m^3 rise in long-term exposure to $PM_{2.5}$ (33). Moreover, an approximately 12% [1; 25] increase in the likelihood of a myocardial infarction per 10 µg/m^3 rise in long-term exposure to PM_{10} has been reported (8). Extrapolating these figures to the population disease burden, fine dust ranks ninth among the most important risk factors in Germany (e32).

Evidence and causality

No single study, however large, permits judgment of causality. Rather, in assessing the existence of a relationship between exposure and effect, international expert panels draw on all published studies in the course of a defined, transparent, and documented process. Studies of different designs with differing strengths and weaknesses are evaluated jointly according to criteria drawn up in advance, contradictory findings are weighed against each other, and, whenever the data permit, the results are summarized in meta-analyses. Furthermore, toxicological and animal studies are scrutinized to assess the existence of biologically plausible mechanisms for the dose–effect relationship in question. The state of knowledge can be evaluated according to the Bradford-Hill guidelines (e11). This also forms the basis of the procedure followed by well-respected organizations such as the International Agency for Research on Cancer (IARC) (e12) and the US National Academy of Medicine/National Academy of Science (IOM/NAS) in determining causal relationships from research findings. The US Environmental Protection Agency (EPA) and the World Health Organization (WHO) avail themselves of similar criteria (e13). Causality is regarded as confirmed in the presence of a relationship for which there are a sufficient number of population studies in which random errors, bias, and other confounders can be largely excluded or which are supported by the results of toxicological studies, especially if these show environmentally relevant concentrations. A causal connection is deemed probable if there are clear indications of causality, but the published data are regarded as too uninformative to fulfill all the criteria for causality. Causal relationships can be inferred in the context of an overall scientific appraisal of purely observational studies together with experimental studies and mechanistic considerations.

Definition of general reference values

The WHO issues advice on concentrations of harmful airborne substances: the WHO Air Quality Guidelines. These recommendations, based on the available evidence from population-based, toxicological, and animal studies, attempt to define levels below which obvious effects on health can no longer be demonstrated. The latest version of the Air Quality Guidelines was issued in 2005 and thus takes no account of the considerable growth in evidence from large prospective studies published in the past 15 years. The 2005 reference value for nitrogen dioxide was set at 40 µg/m^3 on the basis of long-term animal experiments and the population-based studies existing at the time. However, more recent research shows effects below 40 µg/m^3, prompting the European Union (EU) to commission a review of the evidence in 2013. Specifically for nitrogen dioxide, this review showed that health effects can be regarded as confirmed above a threshold value of 20 µg/m^3 (24, e33). Decisive was a meta-analysis of more than 15 long-term studies on nitrogen dioxide (34), which revealed a 5% [3; 8] increase in the risk of death for every 10 µg/m^3 NO_2 (34). As for fine dust, studies with millions of probands have shown clear effects below the current WHO reference value of 10 µg/m^3 for $PM_{2.5}$. A study in the USA, for example, comes to the conclusion that overall mortality in persons over 65 years of age below 12 µg/m^3 $PM_{2.5}$ (the current threshold in the USA) is associated with an increase in mortality of 13.6% [13.1; 14.1] per 10 µg/m^3 $PM_{2.5}$ (e34). The latest figures from Europe, presented in August 2019 at the ISEE annual conference in Utrecht, show even greater effects. At a mean exposure of around 15 µg/m^3 $PM_{2.5}$, mortality (from natural causes) was found to increase by 13% [11; 16] per 5 µg/m^3 $PM_{2.5}$ (e35). Owing to these new research findings, the WHO is currently conducting a comprehensive revision of its recommendations. Publication of the new Air Quality Guidelines is expected in 2020.

Recommendations and standards

The setting of legal standards is a political process that considers scientific recommendations, including the WHO Air Quality Guidelines. The thresholds in the EU, which draw upon the WHO recommendations, are approved by the European Parliament and implemented according to national laws of EU member countries. Thus in 2008 the WHO recommendation for long-term threshold concentrations of nitrogen dioxide (40 µg/m^3) was adopted by the EU, but the recommendation for fine dust was exceeded 2.5-fold. This can best be explained by a combination of political influence and economic considerations, which affect such decisions at the EU level. The regulations in the USA draw upon legally prescribed scientific evaluations that are updated at regular intervals (e9). These region-specific processes result in and explain the large variation in legislation across the world (35). The latest research findings demonstrate the urgent need for action in Europe, especially with regard to

lowering of the standard for fine dust. Switzerland has adopted the 2005 WHO advice on standards for fine dust and implemented a threshold for nitrogen dioxide (30 µg/m^3) that is actually below the WHO recommendation (e36, e37). To date, however, only seven states have passed laws implementing the WHO recommendations for fine dust (an annual mean of 10 µg/m^3 $PM_{2.5}$) (35).

Success can be measured

A study in the USA reported that a lowering of 10 µg/m^3 PM_{10} would be associated with an increase of 6 months in life expectancy (36). Estimates for Denmark show that on average, a 20% reduction in NO_2 would bring about gains of 1.3 to 1.6 years of disease-free life and 0.3 to 0.5 years of overall life expectancy (37). And according to reports from Switzerland (38), improvement of air quality results in decreased medical treatment costs and fewer days absenteeism from work. Ultimately, a society has to decide at what point it pays to take preventive measures. Decisions of this nature are based on cost–benefit calculations in which the economic costs for air quality enhancement have to be balanced against health advantages. Such calculations have been performed, for example, by the EPA and the International Institute for Applied Systems Analysis (IIASA) and show that both in the USA and in Europe, the benefits clearly outweigh the costs (e38, e39). While cost–benefit considerations hold in the USA, in Europe the precautionary principle is applied to decisions on standards. This means that legislative bodies must protect the population from substances that may be harmful, even if the potential for harm has not (yet) been confirmed by research. The current legal thresholds do not live up to this principle, in that obvious health effects occur at sub-threshold concentrations. Further reduction of the standards for harmful airborne substances is thus necessary not only from an economic point of view but also in order to comply with the ethical obligation to protect the general population. Furthermore, most measures to lower air pollution also confer a considerable bonus in terms of climate protection, so that improvement of air quality represents a triple-win situation.

Key Messages

- The term "airborne contaminants in the ambient air" includes, among other substances, fine dust, ozone, and nitrogen dioxide.
- Effects on various organ systems have been observed in population studies, including the cardiovascular system, the lungs, the brain, and the skin.
- Moreover, high rates of preterm birth and diabetes mellitus type 2 have been reported in association with elevated concentrations of fine dust in meta-analyses.
- The current legal standards in Europe do not comply with the precautionary principle, in that health effects also occur at sub-threshold concentrations.
- For the protection of health, the European Union standards should be reduced to well below the current levels (particularly for fine dust <2.5 µm).

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Conflict of interest statement
The authors declare that no conflict of interest exists.

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► **Supplementary material**

For eReferences please refer to:
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eBox 1

Sources and health effects of airborne contaminants

- Fine dust is a mixture of particles <10 µm (0.01 mm) from various sources (1). Combustion processes in motor vehicles, power plants, heating units, and industrial plants produce particulate matter and gaseous substances (sulfur dioxide and nitrogen oxides) which are harmful to health in themselves and combine with agricultural ammonia emissions to contribute to secondary fine dust formation (2). The deleterious effect on health results from chemical and physical properties that produce oxidative stress (on mitochondria, DNA, and proteins) and systemic inflammatory reactions (3). The harmful effect of fine dust on the lungs and airways is undisputed (e2, e3) and connections with cardiovascular disease (4, e2, e4) and some cancers (e5, e6) is regarded as confirmed. Fine dust of natural origin (soil erosion, pollen, micro-organisms) produce allergic and infectious symptoms. Micro-organisms may, however, also contribute to the natural/healthy human microbiome (5).
- Ultrafine particles (<100 nm) play a special role because they penetrate into blood vessels or the autonomous nervous system and may thus even reach the brain. Research is urgently needed, and broad-based routine measurements are lacking.
- Ozone and nitrogen dioxide are irritant gases that also cause oxidative stress (6) and inflammatory reactions in the lungs (7). Ozone forms near the ground due to photochemical processes involving nitrogen oxides and transient organic compounds (8) from incomplete combustion processes. Road vehicles—especially diesel motors—are the principal source of ozone in conurbations (9). In the short term, exposure to ozone leads to airway-related emergency consultations and hospital admissions (e5). Long-term exposure contributes to airway-related mortality and worsening of asthma (10).
- Nitrogen dioxide also worsens the symptoms of asthma (11) and causes airway disease (e8). Recent studies and reviews show an increase in mortality from cardiovascular disease (12, 13, e7, e8) and diabetes(14). It remains open whether NO_2 itself or the mixture of contaminants (for which NO_2 is an indicator) represents the trigger. The epidemiological evidence (14) warrants urgent toxicological studies into the biological mechanisms of action of NO_2 on the cardiovascular system. In a study of diesel gas-exposed rats, cardiac function was impaired despite removal of particulate matter by means of filters (15).

eBox 2

Contamination of indoor air

The air in buildings can also contain considerable concentrations of various harmful substances. The quality of indoor air depends on the ambient air quality outdoors together with any additional sources of contaminants in the interior space. For example, cigarettes, wood-burning stoves, cooking with or without a gas oven, and burning candles can all lead, depending on how the space is ventilated, to considerable increases in the concentrations of fine dust (particulate matter, PM) or NO_2. The deleterious health effects of passive smoking, for instance, have been well researched and the findings have led to legislation forbidding smoking in publicly accessible areas. The World Health Organization and national authorities have issued various recommendations on interior air quality (21, 22). However, respect for privacy means that the laws apply only to those interior spaces that are accessible to the public. This does not as a rule introduce any bias to the analysis of the effects of ambient air pollution, as interior sources have no systematic connection with levels of airborne contaminants outdoors. It is, nevertheless, conceivable that children of socially disadvantaged parents are more exposed to both passive smoking and higher ambient air pollution (because socially disadvantaged families are more likely to live in more polluted parts of town). In such a scenario, a “naive” analysis could systematically confound the effect of the exterior air with that of passive smoking indoors. In high-quality studies, however, this potential confounding of effects is prevented by consideration of social status in study design or analysis. Other interior sources that could be associated through social status with outdoor air concentrations are handled in the same way. However, this is only necessary when indoor exposure is actually associated with outdoor air concentrations.