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# Environmental health risks to children and adolescents: an umbrella review on indoor and outdoor air pollution

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## Executive summary

Children and adolescents are particularly vulnerable to environmental risk factors including air pollution because their brains, lungs and other organs are still developing. Children's breathing rates are higher than those of adults and they inhale more air per kilogram body weight. Because of their smaller height, they breathe air closer to the grounds where some pollutants are emitted, especially from traffic. Children inhale a larger fraction of air through their mouth than adults, which is expected to result in greater air pollution penetration into the lower respiratory tract. Furthermore, their respiratory tracts are more permeable. Additionally, children's bodies and brains are still developing and they have narrower blood vessels, which puts them at particular risk. As their immune system is also still developing, it is weaker than in adults, hence, polluted air can affect children stronger than adults.

In order to present the state-of-the-art knowledge for the health effects for children related to ambient and indoor air pollution, multiple umbrella reviews were conducted. The results of recent most comprehensive and high quality systematic reviews have been systematically evaluated. We considered intervention studies as a special case of evidence generation as it may directly point to solutions to improve the situation. Prioritization of topics among numerous potential health risks and pollutants is based on available evidence, potential health impact on population level, potential individual health risks for exposed children, possibility to conduct interventions and specificity of the topic for children in Europe.

Ambient air pollution is characterized by various pollutants from a wide array of sources. Pollutants can be solid or liquid aerosols (e.g. particulate matters, volatile compounds) or they can be gaseous (e.g. nitrogen dioxide or ozone). The main sectors contributing to emissions of air pollutants in Europe are transport, residential/commercial and institutional energy supply, industry, agriculture and waste management. With respect to health effects, the systematic reviews showed strong evidence for effects of ambient air pollution on mortality, the respiratory endpoints development of asthma, exacerbation of asthma and allergies, decreased lung function and lung function development, and respiratory infections. Evidence from the systematic reviews was moderate for adverse birth outcomes such as preterm birth,low birth weight, and small for gestational age, as well as development of leukemia. A growing body of studies show to date moderate evidence with adverse neurodevelopmental outcomes. There are indications that children exposed to ambient air pollution are restricted in their cognitive development, might show structural changes in the brain and are more likely to be diagnosed with autism. For other outcomes such as cardio-metabolic end-points the evidence was less strong (blood pressure, overweight, changes in glucose metabolism).

About 12% of the children in Europe are regularly exposed to secondhand smoke at home, although since the last two decades, tobacco smoke exposure in public places but also in private settings is significantly decreasing in many European countries. Systematic reviews and meta-analyses provided strong evidence for the development of asthma and severe asthma attacks in relation to secondhand smoke exposure. Overall, there is some reported evidence that postnatal secondhand smoke exposure causes allergic disease. Adverse effects due to prenatal maternal exposure were less consistent. A general challenge is the differentiation between effects from prenatal (maternal) and postnatal SHS exposure since they are often highly correlated and suspect to exposure misclassification.

Formaldehyde has been produced on a large scale for more than 100 years and is used as a binding agent in chipboard and as a preservative in paints, varnishes and cosmetics, as an easy-to-clean additive in textiles, as a disinfectant and in the production of synthetic resin. The main effect of inhaled formaldehyde is irritation of the upper respiratory tract. Studies in children addressed mainly development of asthma or exacerbation of asthma symptoms. Current available studies cannot solve whether there is a causal relationship between indoor formaldehyde exposure and asthma in children.

Every 6$^{th}$ household in European countries is impacted by dampness and mould. The exposures in mouldy indoor environments are complex and diverse. A number of microorganisms, such as mould fungi, yeasts, bacteria, and also mites are related to mould infestation. Furthermore, microbial metabolites and other

microbial substances such as toxins, endotoxins, allergens, β-glucans, microbial volatile organic compounds (MVOC) and microbial fragments such as conidia and fragments of mycelia are commonly found in indoor air and dust. Children are considered to react more sensitively to mould and dampness due to several physiological properties such as the less developed immune system. To date, studies have provided reliable evidence for a number of health outcomes of the respiratory tract including development of asthma, exacerbation of asthma, allergic rhinitis and wheeze in children exposed to mould. Mould exposures tend to be more strongly associated to health outcomes than dampness, and indoor mould-related fungal species tend to lead to more severe health outcome than outdoor related species.

Most outdoor-air interventions aiming to reduce the health impact of both outdoor and indoor air pollution for children at school and at home target at a reduction of motorized traffic emissions and an increase of active transportation. However, measurements of the effect of intervention measures on air pollution concentration and exposure are relatively scarce in the scientific literature. Even less data is available for the health effects. Thus, the benefits are mostly derived indirectly from well-established exposure-response associations. It was found that the creation of a "school street" with a temporary closure of (part of) a street near the school gates, offers benefits for air quality, but also leads to more active commuting to and from school and possibly respiratory health benefits. The siting of a school in a low-pollution area, away from busy roads, seems straightforward in achieving health effects, however this affects the commuting mode being active or passive. Children can reduce the exposure to air pollutants while walking to school along background routes and by avoiding major intersections. A route to school informational intervention seemed effective as the majority of the participants changed their trajectory to school to less polluted routes. Concerning the design of school and childcare facilities, the implementation of green infrastructure such as ivy screen may help to reduce pollutant concentrations and contribute to an improved mental wellbeing of pupils. It is also expected to enhance physical activity and social interactions in playgrounds. The implementation of low-emission zones in many European cities improved ambient air quality, but not to the level of the 2021 WHO Ambient Air Quality Guidelines. Interventions in schools to improve indoor air quality show potential, however the number of interventions that can be implemented in existing schools are limited due to the high costs involved. Interventions are therefore mostly limited to awareness campaigns and ventilation strategies, which show moderate success and rely strongly on the participation and motivation of the occupants of the classrooms. Strict smoking bans at places where children stay is an effective and relevant intervention.

For all evaluated pollutants, the reported effect estimates derived from various meta-analyses are generally small for the individual. However, most of them affect the whole population to some extent. Thus, even a small increase of e.g. asthma risk by around 10% due $NO_2$ (per 10 µg/m³ increased long-term exposure) in the children population is considerable. Thus, the public health impact and the economic costs of ambient air pollution are considerable. In the literature search, we found little data on the assessment of disease burden from these indoor and outdoor pollutants in children. However, these numbers are likely an underestimation since many possible health effects are not well studied. For this review we focussed on well-studied subjects and did not consider topics where the data is scarce such as health effects from carbon monoxide (CO) or volatile organic substances (VOC). It is also well-known that development deficits in childhood may only materialize at old age. For instance, deficits in the lung function or cognition may be compensated in the young age to some extent, but may reach critical threshold at old age earlier than for people with a undisturbed development.

For several pollutants we found indications that socioeconomic status is an important predictor for exposure in the sense that children with lower socioeconomic status are exposed to higher levels of pollutants. This is an important factor that should be considered in future prevention strategies of indoor and outdoor air pollutants.

A key finding of one of our umbrella reviews are the fact that data on the effectiveness of interventions to reduce exposure levels and/or health risks in children are scarce. There is thus an urgent need for a better understanding about which interventions are most useful to prevent environmental health problems. It is

often complex to evaluate the effectiveness of interventions, in particular, if they are restricted to local settings. Nevertheless, policy makers should have an interest to know how effective interventions are and we recommend for the future that introduction of intervention measures are accompanied with a thorough evaluation. In conclusion, the comprehensive review of this report demonstrates that environmental pollutants affect the health of European children and informs about helpful preventive interventions. Although there is still considerably uncertainty about the magnitude of the health risk and about the effectiveness of interventions, preventive actions are warranted. In future reports health effects in children from other research areas such as noise, climate change and chemicals will be dealt with.

**Table 1: Health outcomes with sufficient evidence of health effects from ambient and indoor air pollution**

| Environmental factor | | Health Outcome | |
|---|---|---|---|
| Ambient air pollution [1] | | Mortality | Mortality |
| | | Respiratory outcomes | Infections (ALRI/pneumonia/otitis media) |
| | | | Lung function (acute and growth) |
| | | | Asthma |
| | | | Asthma or allergy exacerbation |
| | | Birth outcomes | Low Birth weight / SGA |
| | | | Preterm Birth |
| | | | SGA |
| | | Neurological | Neuro-development |
| | | | Autism |
| | | | Leukemia |
| Indoor air pollution [2] | Secondhand smoke [3] | Respiratory outcomes | Asthma, wheeze (onset) |
| | | | Asthma attacks/exacerbation |
| | | | LRI |
| | | | Otitis media |
| | | Birth outcomes and developmental effects | SIDS |
| | | | Preterm birth |
| | | | Cryptorchidism |
| | | | Oral clefts |
| | | | Fetal measurements |
| | | | Perinatal death |
| | | Others | Surgical outcomes |

[1] Only outcomes with moderate up to strong strength of evidence in our overall assessment based on existing reviews were included in the summary table. Low to very low levels were excluded.
[2] Note: Health effects of exposure to formaldehyde as well as dampness and mould (as indoor air pollution) were evaluated, but no strong evidence of association was found. Therefore, this is not included in this summary table.
[3] Only outcomes with sufficient strength of evidence in at least one of the considered reviews were included in this summary table.

# 1 Introduction

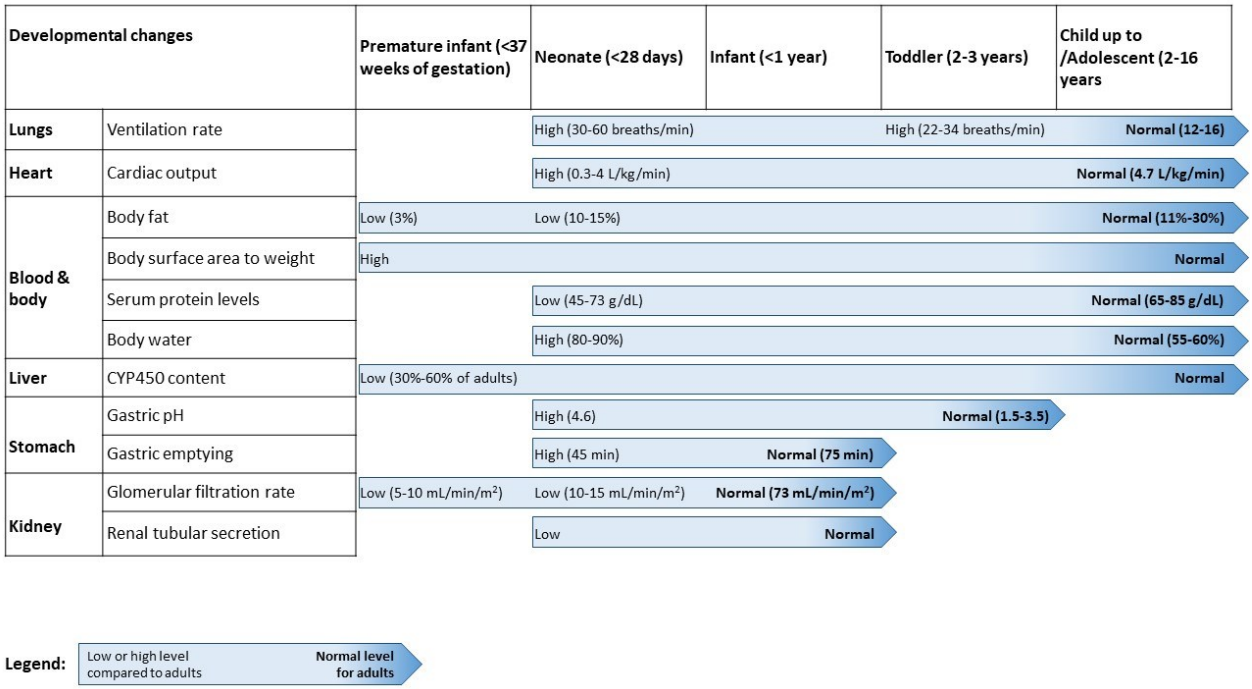
Though most children in the European Union (EU) are generally in good health (4), there are reasons for concern about environmental health risks to children and adolescents in Europe. Not only are they especially susceptible to adverse environmental factors, but increasing evidence shows that they also may be more exposed to many environmental risks, including unsafe home environments; accidents and injuries; road traffic; polluted indoor and ambient air, water, food, and soil; environmental radiation; and noise (5). Ambient air pollution is the main environmental health risk to children in the EU, where it is significantly associated with burden of childhood asthma. Other significant proven sources of environmental burden of disease in children in the EU include secondhand tobacco smoke (SHS), endocrine disrupting chemicals, mould and dampness, and in some locations, lead (6,7). Climate change tends to affect the most vulnerable, including children, disproportionately. Moreover, European youth suffers both the environmental and climate impacts on their health and the eco-anxiety and climate anxiety of present and looming crises (8). Harmful exposures to environmental factors start prenatally (9), and change in nature and intensity throughout childhood and adolescence, at schools, at home and the larger built environment, in a complex network of cause and effect. Furthermore, poor children tend to unsurprisingly be systematically more exposed to and affected by environmental risks (10).

Protecting our children has been frequently cited as a key reason in the political statements (11) accompanying the major EU policies on climate and the environment, though mentions of children in the actual policy documents varies across areas. The Zero Pollution action plan and Chemicals strategy for sustainability (12) both identify them as vulnerable to pollution and specifically target chemical safety in child products, respectively. Climate related major documents such as the EU climate law and the EU adaptation strategy make no explicit mention of children, though they stand to benefit majorly from both efforts, as well as from the building renovation wave strategy (13), the farm to fork strategy (14), and various other efforts under the European Green Deal. Child protection and health related European policies address various aspects of the prevention of environmental health threats to children and adolescents. The EU strategy on the rights of the child (15) aims at ensuring the right to healthcare for all children, including public health and environmental health prevention. The Beating Cancer Plan (16) puts childhood cancer into the spotlight, including prevention, research and monitoring.

The roll out and implementation of all these efforts can be supported by focused, up-to-date facts and figures about the scientifically proven effect of environmental risks on children's health, as well as of the effectiveness of policy interventions. The aim of this task is to provide such facts by first conducting a scoping review of the scientific literature related to indoor and ambient air pollution to identify the key topics and the literature research strategy followed by an umbrella review.

Indoor and ambient air pollution is particularly relevant for children's health for many reasons. Children's breathing rates are higher than in adults and they take in more air per kilogram body weight. Because of their smaller height, they breathe air closer to the grounds, where some pollutants, especially from traffic, are emitted. Their acquired dose is also elevated since they breathe faster and are often more physically active (3). Moreover, children inhale a larger fraction of air through their mouth than adults. Due to their increased amount of oral breathing, they are expected to have greater air pollution penetration into the lower respiratory tract, which is more permeable (17). Additionally, children are still developing their bodies (18) and they have narrower blood vessels, which make them at particular risk. As their immune system is also still developing, it is weaker than in adults, hence, polluted air affects children stronger than adults (19) (Figure 1).

**Figure 1: Development in lungs, heart, blood and body composition, liver, stomach, liver and kidney across pediatric age ranges from premature infant (<37 weeks gestation) to child / adolescent (2-16 years of age). Adapted from the work of Yelleppeddi et al. (20)**




Children and adolescents can be exposed in different settings: at home, in education facilities like schools and during the commute and activities in their spare time. In general, they are likely to be more exposed not only through their increased breathing rate, but also by the fact that they spend more time outdoors and are more active.

Regarding the differentiation between health effects on children and adolescents, our data did not enable us to discriminate between the two age groups. Most longitudinal (cohort) studies make use of birth cohort data. We believe it is a question of funding and feasibility to follow children through the teenage years into adulthood. Thus, there is not much data on teenagers. Despite the lack of data, we very much believe that in case of vulnerability of the brain not only the brain of small children might be affected by air pollution, but also that the time of the remodelling of the brain during adolescence is vulnerable to stressors such as air pollution.

## 2 Methods

We defined five areas of research: a) ambient air pollution, b) secondhand smoke (as subdivision of indoor air pollution), c) formaldehyde (as indoor air pollution), d) dampness and mould (as indoor air pollution) as well as e) interventions for the previous ones. Given the numerous scientific articles and additional amounts of grey literature we performed two kind of reviews for each of the five above mentioned areas of research. Thus, we carried out a scoping review to identify the key topics and the literature research strategy followed by an umbrella review (umbrella+ review in the case of ambient air pollution and interventions). In brief, an umbrella review relies on secondary literature that has already summarized the primary literature; systematic reviews and meta-analyses or reports from agencies such as the US environmental protection agency or UN-reports. In case of umbrella+ review, if we were not able to identify reviews, we additionally ("+") relied on single studies with relevance to the European context. The steps followed in the scoping reviews and the umbrella (+) reviews are described in the chapters below

## 2.1 Scoping review

### *2.1.1 Aim*

The aim of the scoping review is to identify highly relevant environmental health risks of children to be further investigated in an umbrella review. A topic refers to specific outcomes, exposure conditions and possibly age group as incident of asthma in relation to ambient ultrafine particles in infants.

### *2.1.2 Selection criteria*

#### *Literature*

In a first step, it was clarified, which topics in terms of exposure and health outcomes should be covered by the subsequent umbrella review and for which topics original key studies should be included in the review process. For characterizing a topic, we refer to PECO/PICO scheme: population, exposure/intervention, comparison and outcome.

For the scoping review, we heavily relied on the following reports and papers:

- Compendium of World Health Organization (WHO) and other United Nations (UN) guidance on health and environment (21).
- The Lancet Commission on pollution and health, 2018 (22)
- Environmental Burden of Childhood Disease in Europe (7)

For specific main areas of research, we have further considered the following additional key reports (sources) for the selection of relevant outcomes and exposure conditions.

Air pollution:

- LUDOK literature database on health effects of ambient air pollution (www.ludok.ch).
- Integrated Science Assessment of Criteria Air pollutants by the United States Environmental Protection Agency (US EPA) (17,17,23–26).
- Report on Health risks of ambient air pollution in Europe by the WHO HRAPIE project (Health risks of air pollution in Europe) (27).

Indoor air:

- A screening tool for assessment of health risks from combined exposure to multiple chemicals in indoor air in public settings for children: methodological approach (28).
- Chemical pollution of indoor air and its risk for children's health (29).
- Unpublished report of UBA's UKGEP project children and adolescent health in Germany .

#### *Topics*

To select topics, we followed the PECOS and PICOS framework as defined by Cochrane group (30). It helps define the inclusion and exclusion criteria for the population, exposure / intervention, comparator and study design considered:

Population: We defined the eligible age groups to be 0-18. Studies refer to children in general or to certain age groups such as new-borns (<1 month), infants (<1 year), children (1-12 years) and adolescents: (12-18 years). For birth related outcomes, exposure during pregnancy is considered relevant. Exceptionally, higher ages were accepted if age groups could not be disaggregated or if interventions targeting adults lead to health impacts for children. In the case of ambient air pollution, if a study included age groups up to 21, this was also acceptable since these are late adolescents (31).

Exposure/intervention: Within each topic it is defined what type of exposure is relevant. For instance, for air pollution, different types of pollutants may be selected.

Comparator: It is beyond the scope of this review to conduct a meta-analysis, but quantitative statements refer to the question whether a threshold exists, how much the risk is increasing per unit of exposure and whether current regulatory limits are preventing health consequences.

Outcomes: It will be specified which outcomes/diseases are considered.

There are numerous environmental exposures, which may be relevant for the health of children and adolescents. For some of these exposures, research is scarce and thus evidence for risk evaluation is limited. For others, the risk may not be a priority, although it may not be negligible either. Thus, a prioritization is done based on the following criteria:

- Available evidence
- Potential health impact on population level
- Possibility to conduct interventions
- Specific for children and Europe

For potentially relevant topics that have not been considered, the main reasons for non-inclusion are discussed with respect to the criteria above.

We considered intervention studies as a special case of evidence generation as it may directly point to solutions to improve the situation. In the scoping review, we have thus considered intervention topics, which are of high relevance for the health of children and adolescents. We explored intervention research based on the exposures that were identified as relevant for the health of children and adolescents and prioritised as part of the scoping review. Intervention studies and reviews on interventions, where relevant exposures were evaluated, are included in the scoping review. For each type of intervention, the evaluated lifestyle and health outcomes and published evidence are identified.

### *2.1.3 Selected topics*

#### *Ambient air pollution*

Ambient air pollution affects practically all organ systems, and the developing bodies and brains of the unborn child, infants, children and adolescents are at particular risk. Not only does air pollution affect children in this critical phase of development, but they also tend to be more exposed due to different behaviour, breathing patterns and metabolism (Table 2).

## Table 2: Evaluation of priority criteria for various exposure outcome combinations for ambient air pollution

| Pollutant / Source | (Anthropogenic) Emission source | Outcomes | Available evidence | Potential health impact on population level (PAF) | Suitable for interven-tions | European context |
|---|---|---|---|---|---|---|
| $PM_{2.5}$ or $PM_{10}$ | Primary particles: Industrial processes, road traffic, power plants, domestic burning, incineration, resuspension of road and construction dust, secondary particles: formed from precursors | Various short-term and long-term mortality, respiratory, cardiovascular and cognitive endpoints and birth outcomes | Various reviews with different grades of evidence | Unknown but likely to be relevant given high exposure prevalence | yes | yes |
| $NO_2$, NO, NOx | Formed during high temperature combustion of fuels. Main sources are road traffic, domestic heating and power plants. | Various mortality, respiratory and cardiometabolic endpoints (e.g. asthma development, asthma exacerbation, respiratory infections such as pneumonia) | Various reviews and original studies available | Unknown but likely to be relevant given high exposure prevalence | yes | Yes |
| Ozone | Secondary pollutant formed from precursor pollutants $NO_x$ and VOCs from traffic and industrial activities | Short-term exposure associated with respiratory endpoints, long-term exposure possibly with metabolic endpoints though no specific data for children | Various reviews with different grades of evidence | Unknown but likely to be relevant given high exposure prevalence | Yes, indirect | yes |
| $SO_2$ | Formed by burning sulfur containing fuels such as coal or diesel. Power plants, industry, road traffic | Short-term exposure associated with respiratory endpoints, | Comprehensive integrated science assessment USEPA $SO_2$ (24) and various reviews | Unknown but likely to be relevant given high exposure prevalence | yes | Yes |
| CO | Formed during incomplete combustion with lack of oxygen. Main source is road traffic. | Sufficient evidence for cardiovascular effects though not and sufficiently relevant for children / adolescents | Comprehensive integrated science assessment USEPA CO (32) | Unknown but likely to be relevant given high exposure prevalence | yes | yes |
| Black Carbon | Part of PM, formed during incomplete combustion mainly from domestic biomass burning and road traffic | Birth outcomes, cardiovascular and respiratory outcomes, leukemia in children | To be determined | Unknown but likely to be relevant given high exposure prevalence | yes | Yes |
| Benzene | Road traffic | Cancer, respiratory effects and anaemia | Reviews (33,34) | Unknown | yes | yes |

| Pollutant / Source | (Anthropogenic) Emission source | Outcomes | Available evidence | Potential health impact on population level (PAF) | Suitable for interven-tions | European context |
|---|---|---|---|---|---|---|
| Ultrafine particles | Road traffic, airports/aviation, biomass burning industry | Cognitive development and various endpoints | Little research with emerging evidence (17) | Unknown but likely to be relevant given high exposure prevalence | yes | yes |
| VOCs | Industry, traffic | Respiratory effects (symptoms, exacerbation of asthma), neurological effects | Little evidence from ambient air pollution research (34) | Unknown | yes | yes |
| PAH / Benzo(a)pyrene | Domestic heating with biomass / coal, road traffic | Leukemia and other endpoints | Beyond cancer in adults only suggestive evidence (35) | Unknown and multiple exposure pathways (other than ambient air) | | |
| Lead | Traffic and aviation through burning of leaded fuels and metal smelters | Cognitive and other endpoints | Comprehensive integrated science assessment (26,32) | Unknown and multiple exposure pathways (other than ambient air) | yes | yes |
| Other metals in PM (Nickel, Zinc, Vanadium, Iron, Copper, Cadmium, Arsenic) | (Metal) Industry, road traffic, energy sector | Cognitive and other endpoints | Mostly inconsistent evidence on metals other than Nickel, Zinc, Vanadium, Iron, Copper (36) | Unknown | yes | yes |
| Traffic-related air pollution (TRAP) | - | Various outcomes such as respiratory, cardiometabolic, cognitive and reproductive outcomes | Various reviews with different grades of evidence | High since traffic is major source of air pollution in urban contexts | yes | yes |
| Industry | - | Various endpoints | Dependent on pollutant emissions and variable | Small, since point sources | yes | yes |
| Biomass burning | - | Various outcomes such as respiratory, cardiometabolic, cognitive and reproductive outcomes | Few studies for ambient air pollution from biomass burning (36) | Depending on primary source of heating, higher in Northern countries and low and middle income countries | yes | yes |
| Desert dust | - | Same as for PM | Role beyond effects of PM unclear (37) | Unknown | no | Southern European countries more exposed to desert dust events |

Various sources (7,17,23–27,32,33,35,36,38) identified the following air pollutants, that have been widely assessed and related to specific adverse (clinical) endpoints (in children):

- Particulate matter: $PM_{2.5}$, $PM_{10}$
- Oxides of nitrogen: nitrogen dioxide ($NO_2$), NOx, NO
- Ozone
- Sulfur dioxide ($SO_2$)
- Carbon monoxide (CO),
- Black Carbon
- Benzene

Additionally, health effects for the following pollutants are less well documented and the umbrella review – possibly making use of individual studies instead of reviews – needs to clarify whether there is sufficient evidence for health effects of these pollutants on children and / or adolescents:

- Ultrafine particles
- Volatile organic compounds (VOCs) – possibly more an indoor air pollutant
- Polycyclic aromatic hydrocarbons (PAHs) – with benzo(a)pyrene as indicator or reference compound
- Lead and other metals in $PM_{2.5}$

Specific source categories might also be considered for the umbrella review:

- Traffic related air pollution (TRAP)
- Industry
- Biomass burning
- Desert dust

We compiled health effects of ambient air pollution by combining various air pollutants and indirect measures of traffic as exposures and restricting the umbrella review to the following identified health outcomes.

- Mortality
- Respiratory effects: impaired lung function, exacerbation of disease, symptoms, wheeze, asthma development, respiratory infections such as otitis media, pneumonia, acute lower respiratory infections (ALRI), allergies and eczema
- Cardiometabolic effects: increased blood pressure, hypertension, obesity, impaired glucose metabolism
- Birth outcomes such as preterm birth, lower birth weight, small for gestational age, stillbirth, malformations
- Neurocognitive effects: neuro development, diseases autism spectrum disorders and attention deficit syndrome (ADHD or ADD)
- Childhood cancer: leukemia

#### Important risk factors included

***Particulate matter including ultrafine particles and metals found in PM***

Particulate matter is the air pollutant that is most widely studied with various health effects attributed to its exposure ranging from cardiorespiratory effects to neurodevelopmental and metabolic effects. Particulate matter is a mixture of particles most commonly measured as particulate mass of particles with a diameter of 10 µm or less, of 2.5 µm or less, of 1 µm or less or as the number of particles (among others) with submicron width often referred to as ultrafine particles. Particulate matter is emitted as primary particles from industrial processes, road traffic, power plants, domestic burning, incineration, agriculture, resuspension of road and construction dust, or formed as secondary particles from precursors. Important emitters for these precursors are the agricultural sector with its ammonia emissions and nitrogen dioxide

from traffic, household and the industry. Particulate matter contains various components such as organic and inorganic components containing metals, soot / black carbon, aromatic hydrocarbons, inorganic salts or inorganic dust. According to the most recent Global Burden of Disease study for 2019 (39), around 8.6 million DALYs were attributable to ambient $PM_{2.5}$ in the European region. Around 186,000 DALYs were found in the age groups below 20 years of age. Particulate matter $PM_{10}$, $PM_{2.5}$ and ultrafine particles are therefore selected for inclusion into the umbrella review.

***Oxides of nitrogen***

Oxides of nitrogen including $NO_2$, NO and NOx are formed during high temperature combustion of fuels by oxidation of nitrogen from ambient air. They are precursors for the formation of secondary particulate matter and ozone. $NO_2$ is a reactive gas that leads to increased symptoms and emergencies due to respiratory disease and seems to cause asthma. According to the health risk assessment study for air pollution carried out by the European Environment Agency (EEA) (40), 40,400 premature deaths were attributed to long-term nitrogen dioxide exposure in 2019. Therefore, oxides of nitrogen are selected for inclusion into the umbrella review.

***Ozone***

Ozone is a secondary pollutant formed in the atmosphere when heat and light cause chemical reactions from precursor pollutants $NO_x$ and VOCs. These precursors are emitted by traffic and industrial activities, though VOCs are also biogenic. Ozone is a reactive gas that is associated with increased symptoms and emergencies due to respiratory disease and increased mortality as well as metabolic effects. The EEA attributed 16,800 premature deaths to short-term ozone exposure in 2019 (40). Therefore, ozone is selected for inclusion into the umbrella review.

***Sulfur dioxide***

Sulfur dioxide is formed during combustion of sulfur containing fossil fuels such as coal or diesel. Power plants, industry, road traffic are the biggest emitters. Sulfur oxides are also precursors for particle formation in the atmosphere. Sulfur dioxide is an irritating gas to the respiratory system and short-term exposure leads to increased symptoms and emergencies due to respiratory disease. People with asthma, particularly children, are especially sensitive to $SO_2$. Therefore, $SO_2$ is selected for inclusion into the umbrella review.

***Soot / Black carbon***

Black carbon is part of PM, formed during incomplete combustion mainly from domestic biomass burning and road traffic. Black carbon has been widely studied as an important component of PM and important indicator for traffic-related air pollution. Soot is a carcinogenic and short- as well as long-term health effects on cardiorespiratory disease as well as mortality have been described (41).

***Metallic components of PM***

Metals in ambient air such as lead or copper can be components of fuels and emitted by combustion of these or are a result of abrasion and wear of motors, brakes and tires. Important emitters are industries, road traffic and the energy sector. The high oxidative potential of metals and their direct neuro-toxicity in the case of lead are critical characteristics that led to selection of lead, nickel, zinc, vanadium, iron, copper, cadmium, and arsenic for the umbrella review.

***Benzene***

Benzene is a known human carcinogen and an important hazardous air pollutant. Gasoline service stations, motor vehicle exhaust and fuel evaporation, the burning of coal and oil are important emitters of Benzene. Therefore, it was selected for the umbrella review.

#### Risk factors not systematically searched for

***PAHs***

Polycyclic aromatic hydrocarbons PAHs are a group of chemicals with high numbers of single candidates that can have harmful effects on human health. Benzo(a)pyrene is the component that is often used as an indicator for the toxic mixture of PAHs emitted from incomplete combustion of fossil fuels and wood. A recent review by the LTRAP/WHO Task Force on Health (35) identified health effects of PAHs beyond their activity as carcinogen. Even though there were studies indicating effects on the respiratory, cardiovascular and neurological systems and birth outcomes with evidence from mechanistic studies, the evidence was limited. Additionally, it is difficult to disentangle effects from PAH exposure from air from oral intake by roasted foods. Selected substances from this group can be considered if the EEA assigns a higher priority to these chemicals in terms of their risk for children's health.

#### Not selected topics

The CO and VOCs other than benzene are not considered for inclusion into the umbrella review. The evidence for CO beyond clinically relevant cardiovascular effects in adults is only suggestive, but not sufficient, to infer a causal relationship of respiratory effects in children (32). VOCs is a group of highly volatile organic compounds and are considered more an indoor air pollution problem. They are important as precursors for the formation of ozone in ambient air. There might be locally higher exposures in ambient air in industrial zones, but for the general population the exposure in ambient air is considered negligible. Benzene is considered as an important component of the mixture.

The specific sources of air pollution (except traffic related air pollution) are not separately considered in this review since the various selected pollutants cover their most important emissions. Industrial air pollution. Depending on the industry, pollutants and exposures can vary greatly and it is not possible to make general statements on toxicity of industrial exhaust as such. This kind of exposure might well be captured with the generally higher exposure to regulated, classical air pollutants like PM, $NO_2$ and $SO_2$ and specific metals in PM such as Arsenic, Cadmium and Nickel, of which industrial burning of coal, (heavy) oils and waste and partly road transport are important sources (42).

Biomass Burning: While this can be an important source of cancerogenic pollutants such as PAHs, soot and particulate matter, studies that study effects of ambient air pollution as opposed to indoor air pollution through biomass burning on health effects in children are scarce (36).

Desert Dust: Southern European countries are more exposed to desert dust events than Northern countries. Such events can dramatically increase air pollutant levels of particulate matter. According to a review by Tobias et al. (43) short term health effects are found during desert dust episodes in different regions of the world, but in a number of cases the results differ when it comes to associate the effects to the bulk PM, the desert dust-PM, or non-desert dust-PM. These differences are likely due to the different monitoring strategies applied in the epidemiological studies, and to the differences on atmospheric and emission (natural and anthropogenic) patterns of desert dust around the world. A thorough additional review of the evidence is not warranted, since desert dust are covered with health effects of PM. According to the best practice statements form the WHO air quality guidelines (37), interventions include early warning systems to avoid exposure during dust events and regular street cleaning and sweeping to reduce resuspension of dust in streets.

### *Indoor air pollution*

The quality of indoor air is an important health determinant for children and adolescents because they show special characteristics, which increase their vulnerability towards adverse health effects. During this stage of life, the development of organs can also be disrupted by the exposure towards pollutants from indoor air and children show generally higher breathing rates, which increases the uptake of pollutants. Depending on age, children spend most of the time in indoor environments such as schools, day-care centres, kindergartens or their home. Here different sources for indoor air pollution can be found with varying concentrations. Sources of indoor air pollution emissions in general include building materials, furniture and consumer products, combustion processes, smoking, and the penetration of polluted outdoor air. In studies across the European Region, more than 90 chemicals were detected in public settings for children and many have reported concentrations in indoor air exceeding guidance values (34).

To evaluate the health effects of a selected group of indoor air contaminants for the Task 3.2.6.2 key literature was screened and experts from the ETC-HE were consulted. A two-tiered approach was taken to start with indoor air pollution most relevant for public health.

Indoor air can contain a variety of pollutants which at certain concentrations may have adverse effects on human health. Based on expert consultation a list of relevant candidate risk factors in indoor air was composed. This list forms the basis for further prioritization of pollutants for the umbrella review (Table 3).

## Table 3: Candidate list of relevant risk factors / chemicals in indoor air with focus on children's health

| Nr. | Risk factor | Emission source | Health outcomes | Available evidence | Prevalence of Exposure | Potential health impact on population level | Suitable for interventions | European context | Sources |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Secondhand smoke (SHS) / environmental tobacco smoke (ETS) | Cigarette smoke | Respiratory diseases, pneumonia, otitis media (also called middle ear disease/infection), sudden infant death, atopic dermatitis, allergic rhinitis, asthma, learning disability, attention-deficit disorder, attention-deficit/hyperactivity disorder, conductor behavioural disorders, low birth weight, facial clefts | Sufficient evidence available but outcome specific | National household surveys | High | Yes | Yes | (7,44) |
| 2 | Third-hand smoke | Cigarette smoke | Lower respiratory symptoms | Limited | Limited | Medium | Yes | Yes | (45) |
| 3 | Second hand vaping | E-Cigarette vapor | Asthma | Limited | Limited | Limited | Yes | Yes | (46) |
| 4 | Dampness and Mould | Moist indoor environments | Respiratory symptoms, allergies, asthma, perturbation of immunological system | Sufficient evidence available but outcome specific | National household surveys | High | Yes | Yes | (7,47,48) |
| 5 | Volatile Organic Compounds (as a total) | Household products, paints, varnishes, solvents, building materials, disinfectants, personal care products, air fresheners, art and hobby supplies | Irritation of eyes, nose, throat, effects on the nervous system, allergenic or allergy promoting and carcinogenic, mutagenic or reprotoxic effects | Chemical specific | National household surveys | High | Yes | Yes | (28,29,49) |
| 6 | Benzene (VOC) | Activities such as cleaning, painting, mosquito repellents, photocopying and printing. tobacco smoke | Leukemia, cancerogenic effects | Sufficient evidence for causality | National household surveys | Medium | Limited | Yes | (48) |
| 7 | Formaldehyde (VOC) | Smoking, furniture and wooden products, secondary formation | Sensory irritation of the eyes and upper airways, eczema, cancerogenic effects | Sufficient evidence for causality | National household surveys | Medium | Yes | Yes | (7,48) |

| Nr. | Risk factor | Emission source | Health outcomes | Available evidence | Prevalence of Exposure | Potential health impact on population level | Suitable for interventions | European context | Sources |
|---|---|---|---|---|---|---|---|---|---|
| | | from ozone and terpenes | | | | | | | |
| 8 | Ethylbenzene | Gasoline, paints and inks, pesticides, carpet glues, varnishes, tobacco products, automotive products | Carcinogenic effects | Inadequate evidence | National household surveys | Low | Yes | Yes | (50,51) |
| 9 | Toluene | Paints, paint thinners, adhesives, fingernail polish, and gasoline | Effects on the nervous system (mainly due to solvent abuse) | Insufficient for children | National household surveys | Low | Yes | Yes | (52) |
| 10 | Xylene | Automobile exhaust, solvents | Irritation of the skin, eyes, nose, and throat, most studied in high exposure settings | Low level exposure from the environment not expected to cause any adverse health effects | National household surveys | Low | Yes | Yes | (53) |
| 11 | Styrene | Automobile exhaust, cigarette smoke, use of photocopiers | Carcinogenic effects, most studied in high exposure settings | Possible carcinogen | National household surveys | Low | Yes | Yes | (54) |
| 12 | Polycyclic aromatic hydrocarbons (PAH) | Cigarette smoke, consumer articles and mixtures | Carcinogenic effects, intrauterine growth restriction (low birth weight), endocrine-disruptive, neurodevelopmental deficits | Chemical specific | HBM4EU | High | Yes | Yes | (48,55,56) |
| 13 | Naphthalene (PAH, VOC) | Mothballs | Hemolytic anemia | Limited | HBM4EU + National household surveys | Low | Yes | Yes | (48) |
| 14 | Benzo[a]pyrene (PAH) | Combustion Process, cigarettes | Mutagenic and Cancerogenic effects, low birth weight, lung cancer | Sufficient evidence for the cancerogenic effects | HBM4EU + National household surveys | Medium | Yes | Yes | (45) |

### Tier one risk factors

#### Environmental tobacco smoke / Secondhand smoke

Even though sources for indoor air pollution vary widely across Europe many studies have indicated that especially environmental tobacco smoke (ETS) or secondhand smoke (SHS) is one important source with clear evidence on causal relationships with adverse health effects especially in children. SHS in many studies is considered as a single risk factor including a mixture of many toxic single substances such as formaldehyde, benzene or polycyclic aromatic hydrocarbons which all are suspected to be cancerogenic. The impact on population health was estimated in several studies (39,57). According to the most recent Global Burden of Disease study estimates for 2019 (39) around 4.3 million DALYs were attributable to SHS in the European region. Around 220,100 DALYs were found in the age groups below 20 years of age. As the smoking prevalence is still considerable in many European countries, the exposure of children to SHS is still a driving factor for adverse health effects especially for children also influencing their future health. Therefore, the public health impact of SHS is considered to be high and SHS was selected for the umbrella review.

#### Formaldehyde

The International Agency for Research on Cancer (IARC) classified formaldehyde as cancerogenic to humans (Group 1) (58). As a cancerogenic substance formaldehyde still can be found in many indoor environments. The SINPHONIE-study found considerable concentrations of formaldehyde in indoor air samples of schools (59). Children spend a substantial time of their day in schools and can thus be exposed to critical levels of formaldehyde. Despite the cancerogenic effects formaldehyde can cause sensory irritations and many other associations were found in the SINPHONIE-study (48,59). Formaldehyde remains a relevant indoor air pollutant and can have a significant effect on children resulting in a high public health relevance (60). Therefore, formaldehyde as one component of the VOC-group was selected for the umbrella review.

#### Dampness and Mould

Dampness and Mould are other important risk factors in indoor environments. A study of European housing stock showed a prevalence of mould in the last 12 months of about 18% (48,61). Comparable to SHS mould can be seen as a one single risk factor also including a group of harmful microbial substances that can cause adverse health effects in humans. According to the WHO around 29,500 DALYs related to asthma in children (0-14 years) were attributable to mould in 45 European countries in 2008 (62). The link between asthma and dampness and mould exposure identifies these as risk factors of high public health relevance because asthma is highly prevalent in children and adolescents. Because of its importance regarding exposure and health effects dampness and mould was selected as a risk factor for the umbrella review

### Tier two risk factors

VOCs, BTEX (Benzene, Toluene, Ethylbenzene and Xylene) and PAHs are groups of chemicals with high numbers of single candidates that can have harmful effects on human health. In addition to the high number of single chemicals, the health outcomes are also very diverse ranging from irritations to severe cancerogenic effects. For practical reasons these risk factors could be treated as groups, which however limits the value of the review results. Here e. g. the health outcomes resulting from the exposure to these chemicals can vary widely and evaluating the group rather the single chemical might lead to misleading conclusions. Therefore, these groups were selected as tier two risk factors. Selected substances from these groups can be considered, if the EEA assigns a higher priority to these chemicals in terms of their risk for children's health. Single candidates or groupings could otherwise also be considered in the upcoming years of the ETC-HE.

#### Not selected risk factors

- -Third-hand-smoke and secondhand-vaping were not selected because of limited evidence regarding potential health effects on children.
- -Ethylbenzene, Toluene, Xylene and Styrene were not selected either because only very high concentrations lead to adverse health effects or the impact on population health was considered lower as compared to the selected risk factors (see Table 3).
- -Naphthalene and Benzo[a]pyrene form the PAH-Groups were not selected because the impact on population health was considered lower as compared to the selected risk factors (see Table 3).

### *2.1.4 Intervention studies*

#### *Selected topics*

The burden of disease associated with environmental exposures reveals a clear need for interventions to reduce environmental risks and protect the health of children and adolescents. Guidance on policies and interventions for areas of health and environment such as air pollution, climate change and chemicals is provided by the Compendium of WHO and other UN guidance on health and environment (21). However, evidence on the effectiveness of interventions is often lacking. The lack of evidence on early-life population health interventions is also described by the Born in Bradford's Better Start study protocol (63). This experimental birth cohort evaluates 22 population health interventions to improve health and wellbeing of pregnant women, babies, and children of which only two have been tested and proven effective based on robust study designs. Therefore, a systematic approach to the development and evaluation of interventions aiming to reduce air pollution exposure in a European context is required.

Within this scoping review, a number of intervention studies to reduce environmental health risks have been identified based on the environmental risks for children and adolescents that were prioritized above. Table 4 lists these intervention studies to gain insights in the way intervention research is conducted. The interventions are grouped along three main themes: spatial planning, behavioural nudging including educational interventions, building characteristics. The column 'PAF' describes the population to which the described interventions apply. We strived to identify interventions focusing on babies, toddlers, children and adolescents. However, it was assumed that the impact of the intervention also applies to children when the whole population, including adults, was addressed. Rojas-Rueda et al. (7) was identified as a key information source on interventions to reduce exposure to air pollution, secondhand tobacco smoke and dampness.

**Table 4: Candidate list of types of interventions and exposure outcome combinations with focus on children's health**

| Exposure outcome | Intervention | Lifestyle & health outcomes | Evidence of effectiveness | Potential health impact on population level (PAF) | European context |
|---|---|---|---|---|---|
| **Spatial planning** | | | | | |
| Traffic-related air pollution (TRAP) | Shift to active transportation i.e. walking, cycling and public transport | Physical activity (PA)<br>Mortality | A health impact assessment study was identified. Estimates account for air pollution exposure, but no evidence found on the effects of exposure to air pollution (64)<br>Health impact assessment studies were identified (65,66). This evidence includes estimation of changes in $PM_{2.5}$ exposure of the general population and $CO_2$ emissions. | General population | Yes |
| Traffic-related air pollution (TRAP) | Low emission zones and general traffic bans | Mortality<br>Respiratory health | Review papers on the efficacy to reduce air pollution exposure were identified (67,68). In addition, a cross-sectional study evaluated the effect on children's respiratory health (69) | Both the whole population and subgroups such as children | Yes |
| **Behavioural nudging including educational interventions** | | | | | |
| Indoor air (second hand tobacco smoke) | Smoking bans in public spaces | Mortality<br>Morbidity<br>Smoking prevalence | Review publications on studies that evaluated the effects on health and smoking prevalence (70,71) Effects on exposure to second hand tobacco smoke was not addressed specifically. | Both the general population and subgroups such as children | Yes |
| Indoor air (second hand tobacco smoke) | Antismoking media campaigns | Smoking cessation | Before-after study on the effect of the first federally funded US antismoking national media campaign (72) | General population | US |
| Indoor air (second hand tobacco smoke) | Promote smoke-free home environments | e.g. smoking cessation | Review on interventions including randomised controlled trials (73) | Children | Yes |

| Exposure outcome | Intervention | Lifestyle & health outcomes | Evidence of effectiveness | Potential health impact on population level (PAF) | European context |
|---|---|---|---|---|---|
| Indoor air ($CO_2$)<br>Air pollution<br>Heat | School-based awareness campaigns including ventilation | General and respiratory health<br>Educational outcomes | Initiatives have been developed in various European countries (VITO report on Biba study, a before and after study). An interesting framework is provided by the WHO's Healthy School Initiative (74) | Children | Yes |

## 2.2 Umbrella review

### *2.2.1 Aim*

The aim of the umbrella review is to summarize selected evidence on health of children and adolescents in Europe with respect to environmental risks. With umbrella review, we mean that for selected topics where there is a lot of evidence and/or the scope is huge (i.e. chemicals) we will limit the review to key reports and systematic reviews and if available the according meta-analyses. For topics, where there are only few individual studies, we will include original studies of high quality, such as prospective cohort studies with high quality exposure and outcome assessment (umbrella+ review).

### *2.2.2 General approach*

The conduct of the umbrella review will follow a PECOS/PICOS (Participants, Exposures/Interventions, Comparators, Outcomes and Study design) approach. The identified topics in the scoping review will define the exposures to consider and outcomes where already defined.

#### *Inclusion and exclusion criteria*

Table 5 shows the criteria based on population, comparator/effect estimate and study type to be considered in the inclusion or exclusion of literature applying a PECOS/PICOS approach.

**Table 5: General criteria for study inclusion and exclusion based on population, comparator/effect estimate and study type**

| P(E)C(O)S | Inclusion | Exclusion |
|---|---|---|
| **Population** | General human population children and adolescents up to the age of 18 (exceptionally up to the age of 21 for ambient air pollution as late-adolescents and older for interventions if health impacts on children). Both urban and rural at home or school with a preference to studies focusing on Europe and North America.<br>For some topics pregnant women and their unborn children are considered to be relevant | Adult only population studies.<br>Populations exposed in occupational settings except pregnant women. |
| **Comparator** | No exposure or exposure to lower levels of the risk factor in the same or in a referent population. Studies need to have quantified both, the exposure and the corresponding associations including any measure of statistical precision (standard error, confidence intervals). | |
| **Outcome** | Depending on the area of research outcomes may be pre-specified or left open. If left open, umbrella review should discover relevant (new) outcomes | |
| **Study** | Systematic reviews with and without meta-analysis including human studies: cohort studies, case–cohort, case–control, cross–sectional, time series studies, and intervention studies.<br>Reviews that are published (or accepted for publication i.e., in press) between January 2011 (2010 for ambient air pollution) and June/May 2022, written in English.<br>In case of insufficient evidence from systematic reviews, individual studies from Europe might be considered as specified in the corresponding topic pages. | Narrative reviews, qualitative studies, studies reporting only unadjusted results, and clear evidence of an analytical error.<br>Non–human studies (*in vivo, in vitro,* other), controlled exposure (chamber) studies as well as studies with focus on exposure only.<br>Conference abstracts, conference papers, notes, editorials, letters and unpublished data.<br>Umbrella or scoping reviews, burden of disease studies as well as grey literature such as HIAs in countries in the EU. However, these studies will be collected and used as background information/material |

### *Literature search*

#### Databases

Depending on the PECO different databases and sources were searched to optimise adequate and efficient coverage of locating relevant reviews/studies for the umbrella review. We searched PubMed/Medline, Cochrane library and PROSPERO. Reference lists of identified reviews were also used as a source of information. For ambient air pollution, only the special topic database LUDOK was used. For intervention studies, Google Scholar has been used as a source of information.

It is also important to scrutinize high level review reports from international environmental and health agency such as WHO, EEA, EIONET by expert knowledge and checking corresponding websites.

#### Time Frame

Evidence from the latest systematic reviews was considered. Therefore, a time scale of around 10 years (January 2010/2011- May/June 2022) was selected. For ambient air pollution, we searched publications from 1 January 2010 to 9 June 2022 (date of search), while for formaldehyde and mould we searched from 1 January 2011 until 1 June 2022 (date of search) and for SHS from 1 January 2011 until 9 May 2022 (date of search) for formaldehyde and mould; and until 9 May for SHS. For the intervention studies on ambient and indoor air pollution, we searched publications from 1 January 2012 to 31 July 2022 (date of search). Older studies were included only if deemed to be relevant for a specific topic where research output the last 10 years is limited.

#### Conducting the search

The search was conducted by one person per topic.

#### Language

As most of the peer-reviewed literature is published in English, our search was restricted to the English language.

#### Search terms

Based on prior searches for systematic reviews (35,75–77) the following elements of the PECOS search term were decided to be the same for all topics and the PubMed specific search terms can be found in Table 6:

- Population: #1a is used for searching of studies on children of the age of 0-18 years (exceptionally 21 years); in case of pregnancy and fertility related outcomes search term #1b will be considered as well.
- Study type: #2a focusses on systematic reviews and/or meta-analyses, which may be complemented with #2b for topics where cohort studies will be considered as well.

The search strategy used free text in [Title/abstract] (or [tiab]) and [Keywords] and Medical Subject Headings terms [MeSH Terms] related to the elements of the PECOS statement. The search terms within each search grid category were expanded with “OR” and the two categories combined with “AND”.

Search terms for the different topics or exposures were developed separately for each research area (see Appendix A).

For the intervention studies, the search terms were developed separately for each topic (see Appendix A).

**Table 6: General (PubMed) search terms used to characterize population and study type**

| Search No. | Search | Query |
|---|---|---|
| #1a | Population | "Child"[tiab] OR "children"[tiab] OR "pupils"[tiab] OR "preschooler"[tiab] OR "preschoolers"[tiab] OR "student"[tiab] OR "students"[tiab] OR "Adolescent"[tiab] OR "adolescents"[tiab] OR "Infant"[tiab] OR "infants"[tiab] OR "toddler"[tiab] OR "toddlers"[tiab] OR "newborn"[tiab] OR "baby"[tiab] OR "babies"[tiab] OR "boy"[tiab] OR "boys"[tiab] OR "girl"[tiab] OR "girls"[tiab] OR "postnatal*" [tiab] OR "post-natal" [tiab] OR "*school*" [tiab] OR "pediatric*" [tiab] OR "paediatric*" [tiab] OR "prenatal"[tiab] OR "preterm"[tiab] OR "birth"[tiab] OR "gestational"[tiab] OR "pregnancy"[tiab] OR "fetal"[tiab] OR "parturition"[MeSH Terms] OR "Adolescent"[MeSH Terms] OR "Birth Cohort"[MeSH Terms] OR "Child"[MeSH Terms] OR "Infant"[MeSH Terms] |
| #1b | Population | "foetus"[tiab] OR "fetus"[tiab] OR "embryo"[tiab] OR “unborn"[tiab] OR "pregnan*"[tiab] |
| #2a | Study type | "systematic review"[tiab] OR "metaanalysis"[tiab] OR "meta analysis"[tiab] OR "systematic review"[Publication Type] OR "meta analysis"[Publication Type] OR "Meta-Analysis as Topic"[MeSH Terms] |
| #2b | Study type | “cohort” OR “prospective” |

***Data extraction***

The following data were extracted into a table from each review/study:

First author, year of publication, reference, review: databases searched and inclusive search dates, exposures (specific air pollutants) assessed, reported outcomes, (number of primary studies included, study design types), participant characteristics (e.g. new-borns, children age 4-6, etc.), locations, level of comparison (low vs. high exposure or increment), quality appraisal tool used (Newcastle-Ottawa scale or RoB), and authors’ evaluation of overall study quality. If meta-analysis is conducted, the following metrics shall be extracted: summary meta-analytic estimates in the originally reported metric (e.g., odds ratio [OR] or relative risk [RR]), along with their corresponding confidence intervals (CIs) and the related change in exposure. Further, the model of effect estimation used (fixed-effects, random-effects, or both), and measures of heterogeneity such as $I^2$ will be extracted. This list may be complemented if needed for a specific topic.

***Evidence synthesis***

Evidence synthesis was based on most actual systematic reviews and meta-analyses, which are of highest quality. To identify high quality systematic reviews, we considered criteria from AMSTAR2, a tool developed for evaluating the quality of systematic reviews that include observational studies, randomized or non-randomized studies of healthcare interventions (78). Details of these items are described in the supplementary material of Shea et al. (78) and the AMSTAR2 checklist can be found on https://amstar.ca/Amstar_Checklist.php. We did not do a formal AMSTAR2 criteria check, but for ambient air pollution we considered the following criteria: a) the number of databases used for the systematic search (adequacy of the literature search), b) whether a protocol was registered before commencement of the review, c) whether the risk of bias was assessed by any tool, d) the consideration of risk of bias when interpreting the results of the review and assessment of presence and likely impact of publication bias. This allowed an expert judgment on the overall quality of the review.

To rate the quality of the review for the indoor air pollution, we checked the number of literature databases used, whether the risk of bias was assessed by any tool, and whether the authors of the

review followed the PRISMA statement. This allowed to provide an expert judgment on the overall quality of the review. Evidence was then synthesized by a narrative description of the good quality review results including evidence appraisal from the review. For ambient air pollution, where often several reviews were available on the same outcomes, the evidence was summarized in four classifications using the terms strong, moderate, low and very low. The form of the exposure-response or concentration-response relationship was described such as effect thresholds and increase in risk per unit of exposure/concentration, where available. If available, population attributable fractions for the corresponding risk factors were described.

For the umbrella review on interventions, the rating of existing evidence is based on the following procedure:

- Literature searches have been performed in PubMed to identify relevant interventions based on the search terms as defined in the scoping review. The taxonomy of interventions has been further refined based on the results of the searches. The search strings employed are summarized in Appendix A: Search strategy
- Google Scholar searches of the taxonomy of the interventions has been performed, where the first 10 hits have been scanned.
- Our network has been consulted on relevant and grey literature.
- All results are listed in a separate data extraction sheet (Appendix C: Data extraction). The methodology for data extraction is based on the Public Health England review of interventions to improve outdoor air quality and public health (79). Reasons for exclusion are documented in the data extraction sheet (Appendix C: Data extraction).

### *2.2.3 Ambient air pollution*

The LUDOK database maintained by the Swiss Tropical and Public Health Institute on behalf of the Swiss federal office for the environment is a special topic database on health effects of ambient air pollution (www.ludok.ch). Since the LUDOK database covers important journals that are not listed in PubMed but in EMBASE, we searched the LUDOK database, PubMed, and review databases PROSPERO and Cochrane collaboration. Search terms included keywords for children, specific pollutant and exposures, the pre-defined outcomes and the study types (see Appendix A). Table 7 shows specific inclusion and exclusion criteria for exposure to ambient air pollution and the selected health outcomes in addition to the criteria mentioned in the general approach.

**Table 7: Inclusion and exclusion criteria for exposure and outcomes selected for ambient air pollution review**

| P(E)C(O)S | Inclusion | Exclusion |
|---|---|---|
| Exposure | Ambient air pollution with particulate matter air pollution including various measures of ultrafine particles, measures for oxides of nitrogen, ozone, SO2, Soot/black carbon, benzene, the metals (in PM) Lead, Nickel, Zinc, Vanadium, Iron, Copper, Cadmium, Arsenic, traffic related air pollution | Indoor settings and pollutants such as tobacco smoke, other outdoor air pollutants which are not of interest |
| Outcome | Mortality, Respiratory effects (Lung function, Asthma, Emergencies / Exacerbation of respiratory diseases, Respiratory infections), Allergies / Eczema, cardiometabolic effects (blood pressure, hypertension, obesity, impaired glucose metabolism), Birth outcomes, Neurocognitive effects (neuro development, diseases autism spectrum disorders and attention deficit syndrome (ADHD or ADD)), Childhood cancer | |

For screening and documentation of inclusion status, references were imported into EndNote. We uploaded the papers to EndNote for full text screening. For the final documentation, the Endnote References were exported into Zotero.

Studies were included when they studied 1) children, adolescents or pregnant women (for birth outcomes), 2) risk measures of exposure to objectively measured ambient air pollution, 3) on predefined outcomes, 4) in systematic reviews. Exclusion criteria included studies 1) not specific to children or adolescents 2) not on exposure of interest, 3) not reporting on pre-defined outcomes, 4) not using a systematic review approach, 5) not published in English.

Since there was a wealth of systematic reviews of effects of ambient air pollution in children a selection was done following the following criteria:

a. Comprehensiveness, i.e. preference to reviews that included more studies and provided meta-analytical results
b. Use of a risk of bias tools (or comparable methods) and
c. Evaluation of confidence in the quality of the evidence.

The selected references were analysed in depth. We summarized the evidence from one or more reviews for each outcome per pollutant. Since this resulted in lengthy texts, these in depth per pollutant analyses were moved to the Appendix C. An overall summary for each outcome remained together with overview tables on included reviews and a table with meta-analytic summary effect estimates per pollutant where available.

### *2.2.4 Indoor air pollution*

Table 8 shows specific inclusion and exclusion criteria for indoor air pollution in addition to the criteria mentioned in the general approach.

**Table 8: Inclusion and exclusion criteria for selected exposures to secondhand smoke, formaldehyde and mould**

| PECOS - Exposure | Inclusion | Exclusion |
|---|---|---|
| Secondhand smoke | Long–term (months to years) exposure and short-term (day(s)) to secondhand smoke. Measured exposure to secondhand smoke in indoor air. Markers of exposure:<br>• Questionnaire: (self-reported) exposure to secondhand smoke (yes/no)<br>• Numbers of cigarettes smoked<br>• Cotinine level measured in urine<br>Include studies regardless of whether they adjust for co–pollutant exposures. | Cigarette smoke not distinguished from other smoke. |
| Formaldehyde | Long–term (months to years) exposure and short-term (day(s)) to formaldehyde.<br>Measured exposure to formaldehyde in indoor air.<br>Include studies regardless of whether they adjust for co–pollutant exposures. | None |
| Mould | Long–term (months to years) exposure and short-term (day(s)) to mould. Measured exposure to mould (e.g. specific fungi) in indoor air. Markers of exposure:<br>• Questionnaire: (self-reported) exposure to mould (yes/no)<br>Include studies regardless of whether they adjust for co–pollutant exposures.<br>*Mould defined as:*<br>• Mold<br>• Mould<br>• Dampness<br>• Moisture<br>• Humidity (defined as yearly, relative or ambient humidity)<br>• Indoor microbes<br>• Fungi<br>• fungal growth<br>• Airborne micorbial<br>• Indoor spore exposure<br>• Microbial growth<br>• Microbial volatiles<br>• MVOC<br>• mycotoxin | • Mould in food<br>• Mould in breast milk<br>• Fungus as a disease |

Search terms for the selected indoor air pollutants secondhand smoke, formaldehyde and mould are shown in Appendix A.

Due to time constraints and wealth of the literature, it was decided that the selection of the systematic reviews or meta-analyses would be based on the following additional selection criteria:

- Timeliness, i.e. preference to more recent reviews, referring to previously available reviews or including the majority of studies in the previous review assessment.
- Comprehensiveness, i.e. preference to reviews that included more studies.

### *2.2.5 Intervention studies*

For ambient and indoor air quality, interventions are prioritized to define the PICO questions based on their relevance for children and adolescent populations, and the potential availability of substantial evidence:

- Clean air zones around schools;
- Siting of school and childcare facilities and commuter mode and route;
- Design of school and childcare facilities;
- Low-emission zones;
- Indoor air quality in schools: measures and awareness campaigns;
- Interventions to reduce secondhand tobacco smoke exposure;
- Smoking bans.

Table 9 shows the selected PICO (Population – Intervention – Comparator – Outcome) for the selected interventions targeting exposure to ambient and indoor air pollution. It is important to realize that most intervention studies did not directly address changes in health outcomes of children. Such effects are difficult to directly observe unless the study size is very large, the intervention immediate and the latency for health effects short. Thus, most studies addressed changes in environmental pollution and lifestyle, which is informative for the expected health benefits. Physical activity, wellbeing and respiratory health are added to the PICO as lifestyle and health outcomes since these are most relevant to children and adolescents.

**Table 9: PICO for the Umbrella review of intervention studies to reduce exposure to air pollution for children and adolescents**

| Population | Intervention | Comparator | Outcome |
|---|---|---|---|
| Children and adolescents | Clean air zones around schools | Measurements before implementation of the intervention (before-after study) or cross-sectional studies | Air pollution;<br>Noise;<br>Physical activity;<br>Respiratory health |
| Children and adolescents | Siting of school and childcare facilities, commuter mode and route | Measurements before implementation of the intervention (before-after study) or cross-sectional studies | Air pollution;<br>Physical activity |
| Children and adolescents | Design of school and childcare facilities | Measurements before implementation of the intervention (before-after study) or cross-sectional studies | Air pollution;<br>Wellbeing |
| General population | Low-emission zones | Measurements before implementation of the intervention (before-after study) or cross-sectional studies | Air pollution;<br>Respiratory health |
| Children and adolescents | Indoor air quality and schools: measures and awareness campaigns | Measurements before implementation of the intervention (before-after study) or cross-sectional studies | Indoor air (e.g. $CO_2$, PM), spirometry measurements, ventilation rates. |
| Children and adolescents | Reduction of secondhand tobacco smoke exposure | Measurements before implementation of the intervention (before-after study), cross-sectional studies or longitudinal studies | Cotinine (urine, saliva), smoking status, tobacco smoke exposure |
| General population | Smoking bans | Measurements before implementation of the intervention (before-after study) or cross-sectional studies | Secondhand tobacco smoke,<br>respiratory health |

The review of existing evidence from intervention studies is based on the following procedure:

- Literature searches have been performed in PubMed to identify relevant interventions based on the search terms as defined in the scoping review. The taxonomy of interventions has been further refined based on the results of the searches. The search strings employed are summarized in Appendix A: Search strategy
- General google searches of the taxonomy of the interventions has been performed, where the first 10 hits have been scanned.
- Our network has been consulted on relevant and grey literature.
- All results are listed in a separate data extraction sheet (Appendix C: Data extraction). The methodology for data extraction is based on the Public Health England review of interventions to improve outdoor air quality and public health (79). Reasons for exclusion are documented in the data extraction sheet (Appendix C: Data extraction).

# 3 Results and Discussion

The sections below show the results of the umbrella review of each of the considered topics. The scanned literature is available as a list of references in topic-specific Zotero files in the Appendix B. The tables containing the information regarding the data extraction are available in Appendix C.

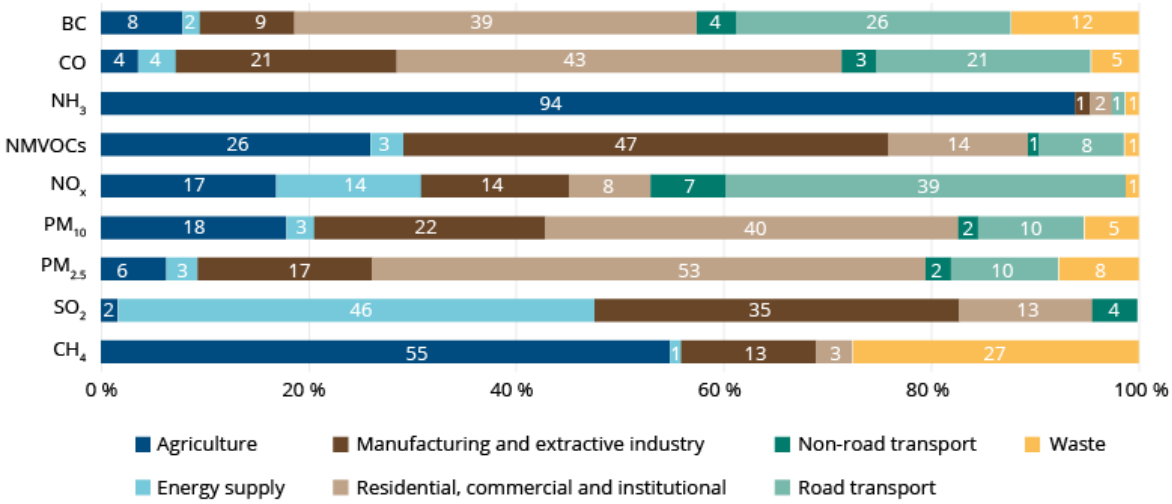
## 3.1 Ambient air pollution

### *3.1.1 Exposure risk characterization and overview of current exposure of and impacts on children and adolescents in Europe*

Ambient air pollution is characterized by various pollutants from a wide array of sources. Pollutants can be solid and liquid aerosols (e.g. particulate matters or volatile compounds) or they can be gaseous (e.g. nitrogen dioxide or ozone). The EU has set limit values for the following key pollutants: particulate matter $PM_{10}$ (particulate matter with a diameter of 10 um or less), nitrogen dioxide ($NO_2$), ozone ($O_3$), sulphur dioxide ($SO_2$), lead, benzene, carbon monoxide (CO). Target values are set for ambient ozone exposure. (EU air quality directive 2008/50/EC) (80) (Figure 2).

The main sectors contributing to emissions of air pollutants in Europe are transport, residential/commercial and institutional energy supply, industry, agriculture and waste (management). In the urban context traffic is an important source of air pollution. In areas where biomass burning like wood combustion is wide-spread, households are important sources. People are exposed to air pollution in urban and rural areas. Depending on the pollutant, different sources are the main drivers of exposure(81). The main places of children's and adolescent's exposure to ambient air pollution are in their neighbourhood, close to their homes, at day-care, kindergartens or schools, on the way between these places and to a lesser extend where recreational activities take place (82). Their exposure is a combination of the actual exposure levels and the time spent in each micro-environment.

**Figure 2: Percentages of contribution to primary emissions of air pollutants per pollutant source (80)**




Air pollution has generally improved over the last decades in Europe. Mostly Western and Northern European countries made further progress in the reduction of air pollution exposure (83) (Figure 3) . This trend is also seen in the more polluted and more densely populated urban areas. However, in regions characterized by highly polluting industries and energy generation e.g. based on coal such as Eastern and South-eastern European countries, levels $PM_{2.5}$ tend to be higher and reduction trends are not as steep (84) (Figure 4).

**Figure 3: Annual mean values of $PM_{10}$ per country 2013-2020/21 (82)**

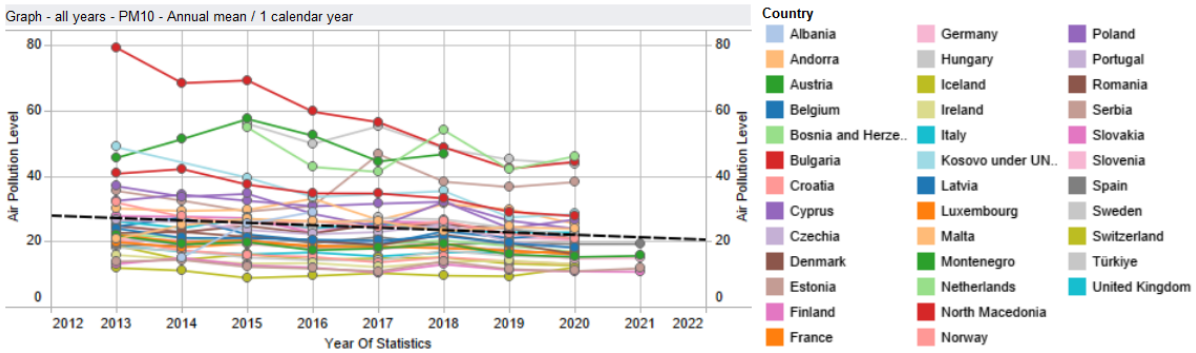
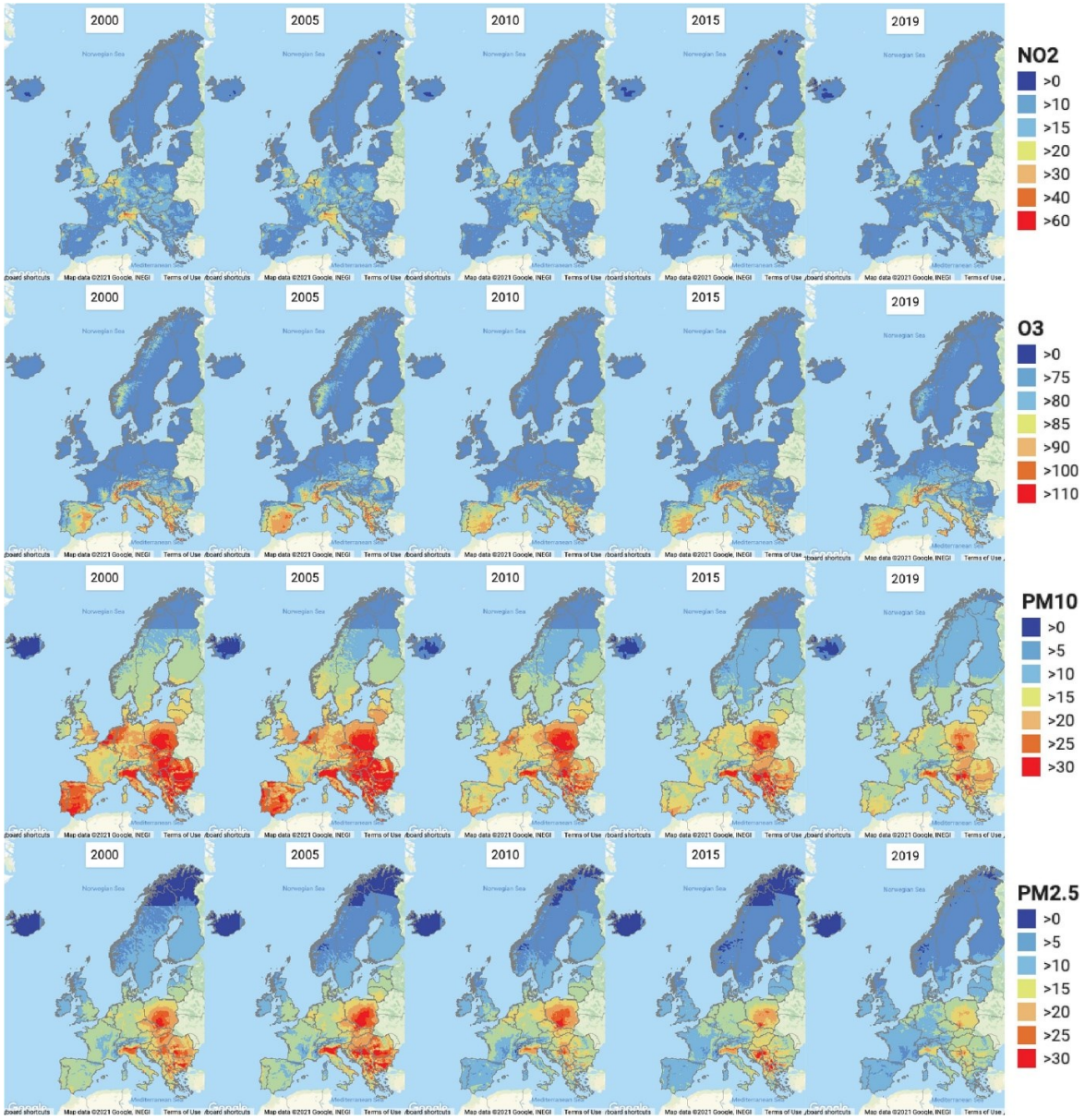


**Figure 4: Europe-wide annual average ground-level NO2, O3, PM10, and PM2.5 concentrations (µg/m3) estimated by GTWR00-19 in 2000, 2005, 2010,2015, and 2019 (83)**




Despite this progress, air pollution at current levels is still harmful to human health. Not only has the evidence on new health effects beyond the respiratory and cardiovascular system improved, but also the understanding of health effects at very low levels has increased (86). In 2021, the WHO has published new health based air quality guideline values (37) (Table 10). Since the WHO air quality guidelines are set to protect all people from air pollution including the young, the elderly and the vulnerable, the guideline values are also applicable to children.

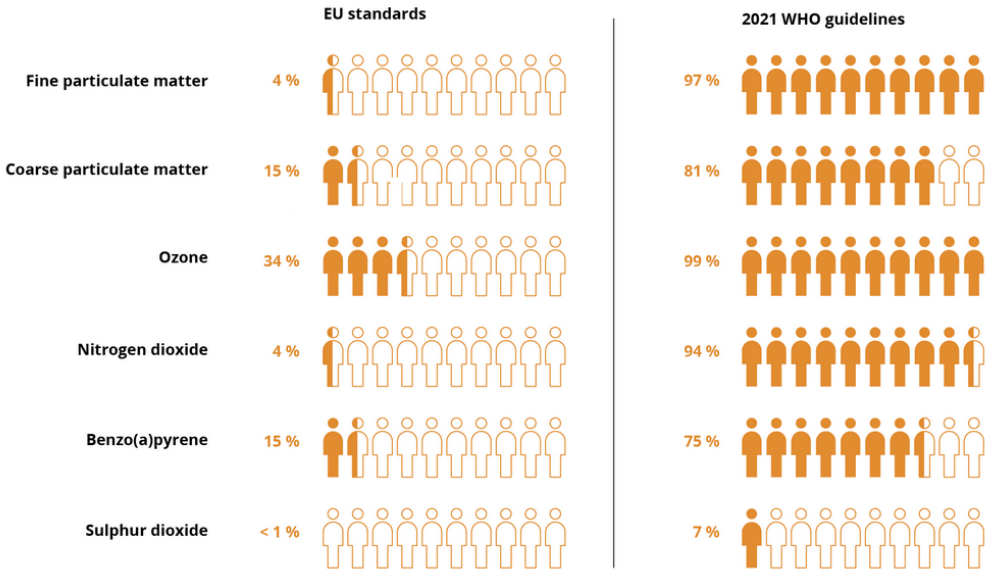
**Table 10: WHO Air quality guidelines 2005 and 2021 compared to the EU limit and target values as defined in the Directive 2008/50/EC (80)**

| Pollutant | Averaging time | 2005 AQGs | 2021 AQG level | EU Directive |
|---|---|---|---|---|
| $PM_{2.5}$, µg/m³ | Annual | 10 | 5 | - |
| | 24-hour[a] | 25 | 15 | - |
| $PM_{10}$, µg/m³ | Annual | 20 | 15 | 40 |
| | 24-hour[a] | 50 | 45 | 50 |
| $O_3$, µg/m³ | Peak season[b] | – | 60 | - |
| | 8-hour[a] | 100 | 100 | (Target: 120) |
| $NO_2$, µg/m³ | Annual | 40 | 10 | 40 |
| | 24-hour[a] | – | 25 | (1h: 200) |
| $SO_2$, µg/m³ | 24-hour[a] | 20 | 40 | 125 |
| CO, mg/m³ | 24-hour[a] | – | 4 | (8h 10) |

µg = microgram
[a] 99th percentile (i.e. 3–4 exceedance days per year).
[b] Average of daily maximum 8-hour mean $O_3$ concentration in the six consecutive months with the highest six-month running-average $O_3$ concentration.
Note: Annual and peak season is long-term exposure, while 24 hour and 8 hour is short-term exposure.

Thus, the population – including children – exposed to harmful levels of air pollution has yet increased due to the lower air quality guideline levels that define "safe" levels of air pollution, set by the WHO in 2021. According to the EEA (2022), 97% of the urban population in the EU was exposed in 2019 to concentrations of fine particulate matter ($PM_{2.5}$) above the new WHO guideline level of 5 µg/m³ (Figure 5).

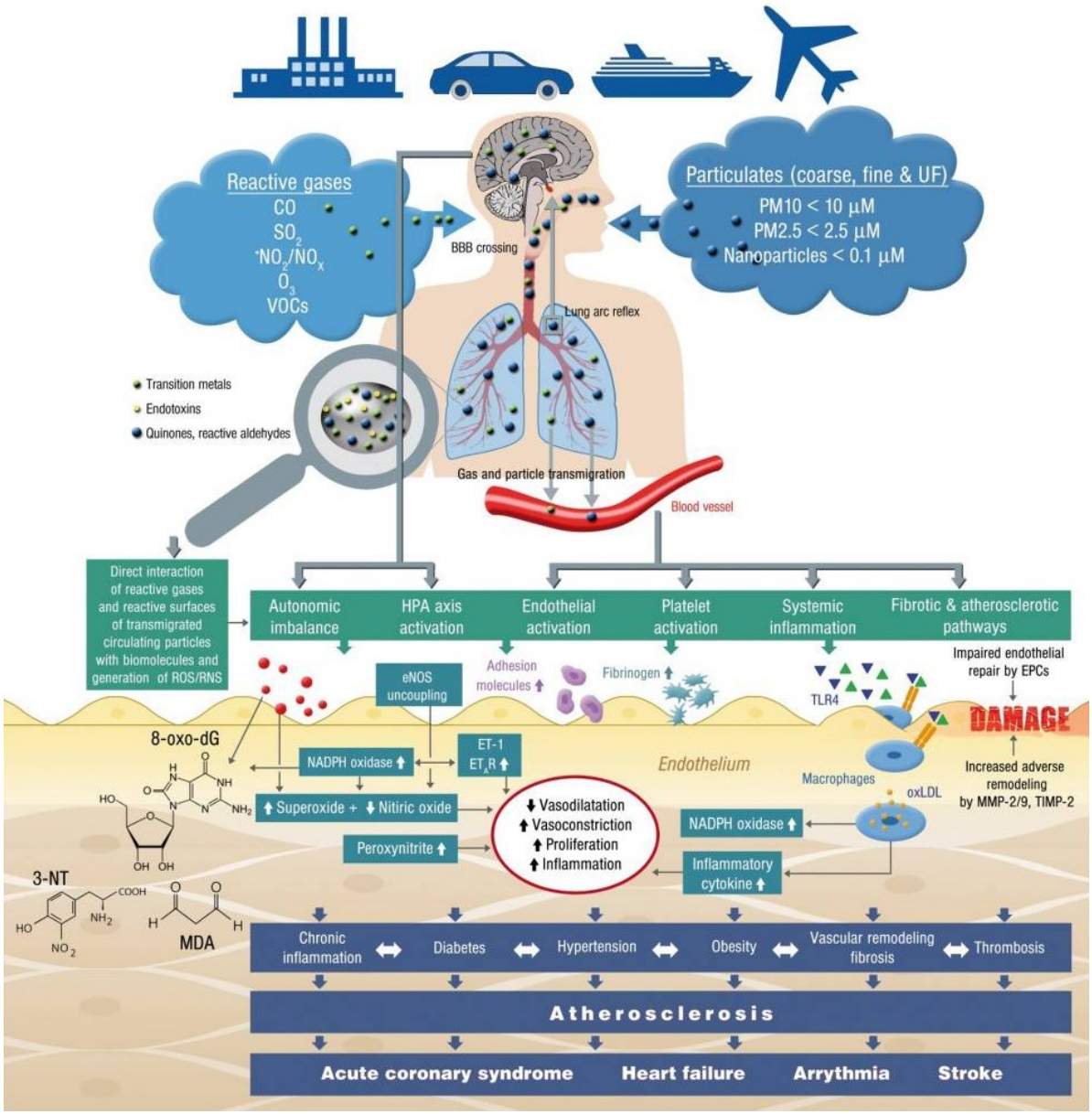
**Figure 5: Share of the EU urban population exposed to air pollutant concentrations above EU standards and WHO guidelines in 2019 (86)**



Furthermore, concentrations of ozone and nitrogen dioxide often do not comply with those new WHO guideline values. In particular, ozone concentrations are very weather dependent, which makes the identification of trends across years difficult. Therefore, the majority of European population is still exposed to air pollution levels that are harmful to their health and wellbeing. Ambient air pollution can affect practically all organ systems.

Various biological mechanisms are known to play a role from exposure to health effects. Most pollutants are irritants and can have an immediate and direct effect on the respiratory tract triggering cough, shortness of breath and exacerbation of pre-existing conditions like asthmatic attacks and chest pain. Moreover, long-term exposure induces oxidative stress and the generation of reactive oxygen species that can lead to imbalances in the autonomic nervous system, the blood coagulation and fibrinolysis system, as well as the immune system (87) (Figure 6).

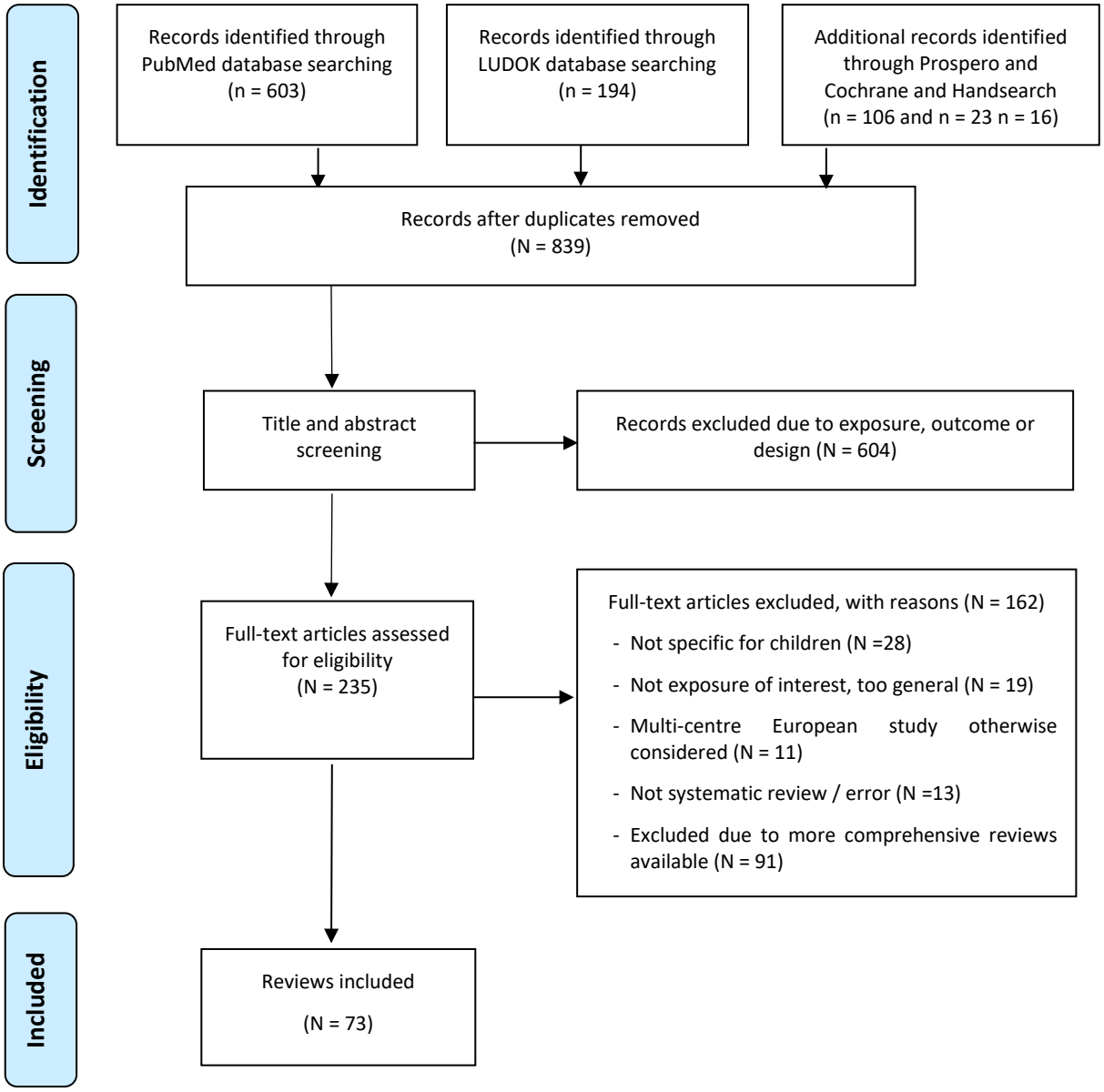
**Figure 6: Underlying mechanistic pathways from air pollution exposure to cardiovascular disease, which can be applied to other health endpoints throughout the body (85)**



### 3.1.2 Study search and selection

The search in these four databases yielded 836 studies after removal of duplicates (see PRISMA Chart in Figure 7). After careful screening of titles and abstracts, considering inclusion and exclusion criteria, 604 studies were removed, leaving 235 studies for full text analysis. The number of reviews per outcome category was high, especially for birth outcomes Figure 8). Basic data were extracted to select the reviews with the most comprehensive data, leaving 73 reviews for the umbrella review. Therefore, 44 (60%) included meta-analyses in their systematic reviews.

**Figure 7: PRISMA flow diagram for the search of selected health effects on children due to ambient air pollution. Search date 9.6.2022**



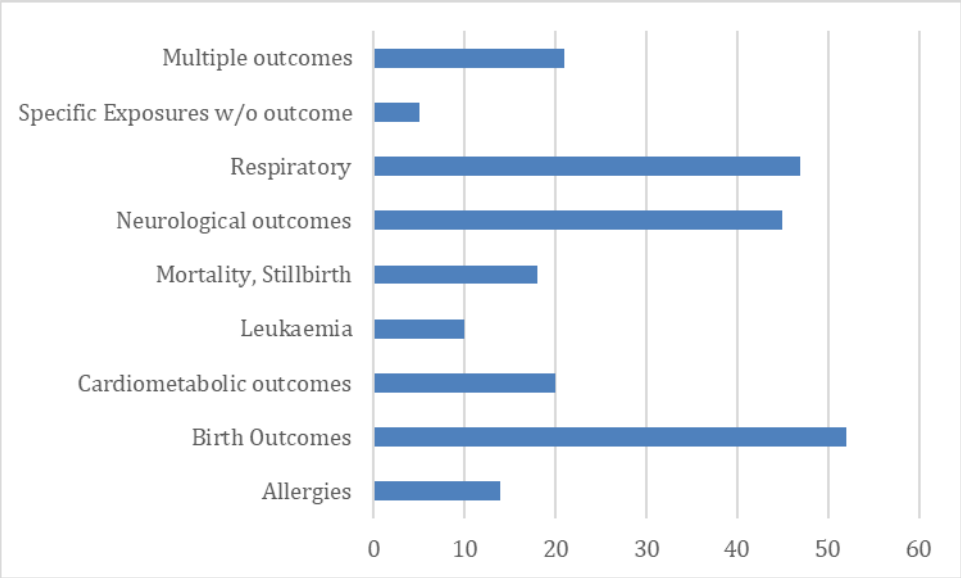

### 3.1.3 Study characteristics and quality assessment

Detailed characteristics of the included reviews were extracted and are shown in each chapter with the first table summarizing the pollutants studied and main results of the reviews including the evidence level as judged by the authors, where available. A second table describes the specific

outcomes, the pollutants studied, the number of primary studies included as relevant criteria from the selection process including the search dates, the number of databases searched, the origin of studies as well as the quality assessment tools used, when this information was available. When meta-analytical results were available, we compiled these in a third table with information on the increment used for the analysis, the number of studies or effect estimates included in the analysis, the magnitude of the effect including the confidence intervals as well as measure of heterogeneity and p-values and the results of publication bias analyses.

Of note is that the literature regarding health effects of ambient air pollution is highly influenced by European and North America n studies. Thus, the majority of individual studies that was included in the reviews reported effects on populations in Europe or comparable populations in North America (see column on "Origin of studies" in the second table of each health outcome chapter).

**Figure 8: Distribution of studies in the full-text screening according to main outcomes studies (n=235)**




### *3.1.4 Health outcomes and evidence*

#### *Mortality*

One recent review by Kihal-Tlantikite et al (88) examined infant mortality. This review relied on searches of one database only and included 24 studies published between 2000 and February 2019. Over half of the studies were from a context comparable to Europe in terms of air pollution sources and levels, with five studies contributing from Europe. Quality of the studies was not assessed, however a meta-analysis with 14 studies was conducted. We included the reviews by Orellano et al. (89,90) conducted for the development of the WHO air quality guidelines (2021) on short-term all-cause and cause-specific. These reviews were of high quality and included the whole age range reporting on subgroup analysis for children and adolescents. The review on $SO_2$ included 67 studies including 5 specific for children for $SO_2$ (90) and 167 studies on short-term effects with particulate matter, $NO_2$ and ozone (89). Meta-analysis was conducted and the certainty of evidence was assessed using a specifically for the WHO guideline process developed adaptation of GRADE. (see Table 11 to Table 13 below).

Overall, the included review found significantly increased mortality risks for infants in long- and short-term studies. Statistical significance refers to the probability that the observed result could have occurred randomly if it has no true underlying effect. Thus, the results point towards a true underlying effect of ambient air pollution. The quality assessments and evidence synthesis also indicate a strong evidence base. Additional evidence on infant mortality stems from reviews conducted for the WHO

guideline process (37). Only the reviews on short-term associations with mortality mentioned or reported subgroup results for children, which showed significantly higher effect estimates in children than in adults or elderly in the $SO_2$ analysis. Subgroup results for the short-term associations with particulate matter, $NO_2$ and ozone were not significantly different. We assume that the long-term effects on mortality in children are also comparable to effects reported in the WHO reviews by Chen and Hoek (91) for PM and Huangfu and Atkinson (92) for $NO_2$ and ozone. The evidence for all-cause mortality was rated as high for all pollutants and exposure windows. The UN reports also list deaths related to complications of low birth weight and preterm birth as well as respiratory diseases including pneumonia as important endpoints especially related to particulate air pollution (19,33,93). Even though, we lack reviews on childhood and adolescent mortality, we believe the association of mortality that has been reported for the entire population with a strong evidence base also from European and North American studies, to be true also for (older) children and adolescents. We believe the evidence to be strong.

**Table 11: Results of the included reviews on childhood mortality attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant(s) (focus) | Selected results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| Infant mortality | Kihal-Tlantikite (2020) | LT: PMs, $NO_2$ | The majority of studies showed increased mortality risk with the particulate matter pollution and null associations with $NO_2$- The risks of post-neonatal mortality and sudden infant death syndrome were significantly increased with $PM_{10}$ exposure. | NR | (88) |
| All-cause mortality | Orellano (2021) | ST: $SO_2$ | Increased all-cause mortality risk with short-term exposure to $SO_2$ also found in subgroup analysis of children studies | moderate | (90) |
| All-cause mortality | Orellano (2021) | ST: PMs, $NO_2$, ozone | Overall analysis for all age groups including up to 66 studies showed increased mortality risks with short-term exposure to particulates, $NO_2$ and ozone with high quality of evidence. Subgroup analysis by age did not show statistically different results, indicating increased risks for children as well. No estimates reported for the subgroup analysis | high for all pollutants | (90) |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 12: Characteristics of included reviews on childhood mortality attributed to ambient air pollution**

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search date up to | DB searched | Publication year range | Origin of studies | Quality-tool |
|---|---|---|---|---|---|---|---|---|---|
| Infant mortality | Kihal-Tlantikite (2020) | LT: PMs, $NO_2$ | yes (14) | 24 | 2000-Feb 2019 | 1 | 2000-2018 | North America (7), South America, Europe (5), Asia, Africa | none |
| All-cause mortality | Orellano (2021) | ST: $SO_2$ | yes | 67 (5 children) | - Dec 2018 | 7 | | North America, South America, Europe, Asia, Africa | WHO-GRADE |
| All-cause mortality | Orellano (2021) | ST: PMs, $NO_2$, ozone | No results for children | 196 (38 children) | - Sep 2018 | 7 | 1992-2019 | North America, South America, Europe, Asia, Africa | WHO-GRADE |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 13: Summary estimates from meta-analyses from selected reviews on childhood mortality attributed to ambient air pollution**

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric [HR, OR, RR] | Estimate | 95%-CI | Model [fixed / random - effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| All cause infant mortality | LT: $PM_{10}$ | Kihal-Tlantikite (2020) | 10 µg/$m^3$ | 9 | OR | **1.01** | **1.00, 1.02** | RE | 47.20% | 0.057 | low probability of PB |
| All cause infant mortality | LT: $NO_2$ | Kihal-Tlantikite (2020) | 10 µg/$m^3$ | 5 | OR | 1.00 | 0.99, 1.02 | FE | 0% | 0.985 | low probability of PB |
| Respiratory infant mortality | LT: $PM_{2.5}$ | Kihal-Tlantikite (2020) | 10 µg/$m^3$ | 4 | OR | 1.37 | 0.94, 2.00 | RE | 65% | 0.033 | low probability of PB |
| Respiratory infant mortality | LT: $PM_{10}$* | Kihal-Tlantikite (2020) | 10 µg/$m^3$ | 4 | OR | **1.13** | **1.01, 1.27** | RE | 76.40% | 0.005 | low probability of PB |
| Sudden infant death syndrome | LT & ST: $PM_{2.5}$ | Kihal-Tlantikite (2020) | 10 µg/$m^3$ | 4 | OR | 1.08 | 0.93, 1.26 | NR | 0% | 0.402 | low probability of PB |
| Sudden infant death syndrome | LT & ST: $PM_{10}$ | Kihal-Tlantikite (2020) | 10 µg/$m^3$ | 5 | OR | **1.04** | **1.01, 1.08** | NR | 31.50% | 0.212 | low probability of PB |
| All-cause mortality | ST: $SO_2$ | Orellano (2021) | 10 µg/$m^3$ | 4 | RR | **1.062** | **1.039, 1.085** | RE | NR | <0.01 | NR |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

*Reading example for the association of infant respiratory mortality with long-term $PM_{10}$ exposure: (Kihal-Tlantikite, 2020): the mortality risk was significantly increased by 13%, with a confidence range of the true effect between 1-27% for a 10 µg/$m^3$ higher long-term $PM_{10}$ exposure. Heterogeneity $I^2$ of study results was high, indicating a high between study variation. Publication bias was not detected. The risk estimate is >1.00 and the lower level of the 95% confidence interval is >1.00, thus the risk associated with the pollutant is statistically significant. Statistical significance (indicated as bold effect estimates) refers to the probability that the observed result could have occurred randomly if it has no true underlying effect. If an estimate is significant, such random occurence is unlikely.

### *Birth outcomes*

#### Stillbirth and spontaneous abortion

Three reviews were included (see Table 14 to Table 16 below), two of them investigated spontaneous abortion (defined as spontaneous loss of a fetus within 180 days of gestation) and two stillbirth (defined as delivery of a fetus showing no signs of life with a birth weight <1000 g and at least more than 20 weeks of gestation). The most recently published review by Zhu et al. (94) studied the association between spontaneous abortion and long-term exposure to $PM_{10}$ and $PM_{2.5}$. They included 6 studies published between 2018 and 2021. GRADE was applied for quality assessment of the studies and a meta-analysis was conducted. Grippo et al. (95) was also included, since they investigated the association between spontaneous abortion (and stillbirth) with $NO_2$, CO, $SO_2$, ozone and cooking smoke. They found 22 studies for spontaneous abortion. However, they did not conduct a meta-analysis or a risk of bias assessment. A more recent publication from Zhang et al. (96) found 15 studies on stillbirth and the exposure to particulate matter, $SO_2$, $NO_2$, CO and ozone published up to December 2020. The Newcastle Ottawa Scale and the risk of bias assessment tool from OHAT was applied for quality assessment. In addition to those three reviews, we also included results from an umbrella review by Nyadanu et al. (97). They included 36 reviews on birth outcomes and particulate matter, carbon monoxide, ozone, $SO_2$ and $NOx/NO_2$, three of them on stillbirth and two on spontaneous abortion. Evidence was assessed with the JBI critical appraisal tool.

There is moderate evidence for an association between spontaneous abortion and particulate matter. Increased risk for still birth associated with PM was also reported, however the evidence has not been rated yet. The included umbrella review by Nyadanu et al. (97) also found a more consistent positive association for spontaneous abortion and particulate matter, whereas the association with stillbirth was less consistent. The evidence was classified as *probable* due to the high heterogeneity and imprecision. The number of high-quality (cohort) studies with consistent results is still small. Furthermore, biological mechanisms and potential pathways remain to be clarified and none of the reviews was able to perform dose-response functions. We therefore consider the evidence base to be suggestive for SAB and stillbirth.

It should be noted that significantly elevated meta-analysis results are only one of several elements that contribute to confidence in results. Additional elements such as risk of bias, heterogeneity of studies or number of studies are considered for the assessments.

**Table 14: Results of the included reviews on spontaneous abortion and stillbirth attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant(s) (focus) | Selected results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| Spontanous abortion | Zhu (2022) | LT:$PM_{10}$, $PM_{2.5}$ | Consistent evidence from limited number of studies for an association of SAB with $PM_{2.5}$ and $PM_{10}$ | moderate | (94) |
| Stillbirth (after 20 weeks of pregnancy) | Zhang (2021) | ST/LT: PMs, $SO_2$, $NO_2$, CO, ozone | Indication for an association between stillbirth and short-therm ozone and long-term $PM_{2.5}$ and CO | NR | (96) |
| Spontanous abortion, stillbirth | Grippo (2018) | PMs, $NO_2$ (6), CO, $SO_2$, Ozone, cooking smoke | Most consistent results for an association with SAB and stillbirth was found for PM | NR | (95) |
| Stillbirth (after 20 weeks of pregnancy) | Nyadanu (2022) | $PM_{2.5}$, $PM_{10}$, $NO_2$, $SO_2$, CO, ozone | more consistent positive association for spontaneous abortion and particulate matter | NR | (97) |
| Spontanous abortion | Nyadanu (2022) | $PM_{10}$, $PM_{2.5}$ | less consistent positive association for spontaneous abortion and particulate matter | NR | (97) |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 15: Characteristics of included reviews on spontaneous abortion and stillbirth attributed to ambient air pollution**

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search date up to | DB searched | Publication year range | Origin of studies | RoB tool |
|---|---|---|---|---|---|---|---|---|---|
| Spontanous abortion | Zhu (2022) | LT:$PM_{10}$, $PM_{2.5}$ | yes | 6 | Feb 2021 | 3 | 2018-2021 | North America (3), Europe (1), India, Iran | GRADE |
| Stillbirth (after 20 weeks of pregnancy) | Zhang (2021) | ST/LT: PMs, $SO_2$, $NO_2$, CO, ozone | yes | 15 | Dec 2020 | 4 | 2007-2020 | Europe (1), North America (7), Asia (5), other (1) | NOS, OHAT |
| Spontanous abortion, stillbirth | Grippo (2018) | PMs, $NO_2$ (6), CO, $SO_2$, Ozone, cooking smoke | no | 35 (human studies), 4 both, 17 abortion, 22 stillbirth | Mar 2018 | 1 | NR | Europe (7), North America (4), Asia (18), other (6) | none |
| Stillbirth (after 20 weeks of pregnancy) | Nyadanu (2022) | $PM_{2.5}$, $PM_{10}$, $NO_2$, $SO_2$, CO, ozone | | 36 reviews (21 with meta):295 primary studies | Mar 2022 | 6 | NR | Overall review: North America (125), Europe (52), Asia (70), other (48) | JBI |
| Spontanous abortion | Nyadanu (2022) | $PM_{10}$, $PM_{2.5}$ | | 36 reviews (21 with meta):295 primary studies | Mar 2022 | 6 | NR | Overall review: North America (125), Europe (52), Asia (70), other (48) | JBI |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 16: Summary estimates from meta-analyses from selected reviews on spontaneous abortion and stillbirth attributed to ambient air pollution**

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric [HR, OR, RR] | Estimate | 95%-CI | Model [fixed / random - effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Spontanous abortion | $PM_{2.5}$ | Zhu (2022) | 10 µg/m$^3$ | 5 | RR | **1.2** | **(1.01-1.40)** | RE | 0.986 | <0.001 | no indication of publication bias |
| Stillbirth (after 20 weeks of pregnancy) | third trimester $PM_{2.5}$* | Zhang (2021) | 10 µg/m$^3$ | 5 | OR | **1.094** | **(1.008-1.180)** | FE | 0.748 | 0.003 | no substantial bias detected |
| Stillbirth (after 20 weeks of pregnancy) | thrid trimester CO | Zhang (2021) | 10 µg/m$^3$ | 5 | OR | **1.0009** | **(1.0001-1.0017)** | FE | 0.703 | 0.009 | no substantial bias detected |
| Stillbirth (after 20 weeks of pregnancy) | entrie pregnancy $PM_{2.5}$ | Zhang (2021) | 10 µg/m$^3$ | 7 | OR | **1.103** | **(1.074-1.131)** | FE | 0.621 | 0.015 | no substantial bias detected |
| Stillbirth (after 20 weeks of pregnancy) | first trimester ozone | Zhang (2021) | 10 µg/m$^3$ | 6 | OR | **1.028** | **(1.001-1.055)** | FE | 0.735 | 0.002 | no substantial bias detected |
| Stillbirth (after 20 weeks of pregnancy) | lag 4 ozone | Zhang (2021) | 10 µg/m$^3$ | 4 | OR | **1.002** | **(1.001-1.004)** | FE | 0.327 | 0.216 | no substantial bias detected |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

*Reading example for the association of stillbirth with third-trimester $PM_{2.5}$ exposure: (Zhang, 2021): the stillbirth risk was **significantly** increased by 9%, with a confidence range of the true effect between 0.8 and 18% for a 10 µg/m$^3$ higher $PM_{2.5}$ exposure. Heterogeneity $I^2$ of study results was high, indicating a high between study variation. Publication bias was not detected. Statistical significance (indicated as bold effect estimates) refers to the probability that the observed result could have occurred randomly if it has no true underlying effect. If an estimate is significant, such random occurence is unlikely.

#### Preterm birth

One review by Yu et al. (98), one umbrella review by Nyadanu (97) and the integrated science assessments of the US EPA for ozone (23) were considered because they are of good quality, searched for multiple databases, conducted a meta-analysis and assed the level of evidence (see Table 17 to Table 19 below). Additionally, we included the US EPA ISA for carbon monoxide from 2010 (32) due to its very detailed assessment of the evidence. The most recent review by Yu et al. (98) included 77 long-term and 13 short-term studies on the association between preterm birth and particulate matter published between 2000 and 2021. The evidence was evaluated with GRADE. Nyadanu et al. (97) included 36 reviews on birth outcomes and particulate matter, carbon monoxide, ozone, $SO_2$ and $NOx/NO_2$, seven of them on preterm birth and used the JBI critical appraisal tool to assess the evidence. The US EPA ISA on ozone (23) included 22 new studies since the US EPA ISA on ozone from 2010, searched until March 2018, adding up to 29 studies. The ISA on CO (32) found seven studies published from 2000 to 2007. The HEI TRAP review (99) and US EPA ISA on PM (17) were reference to support the overall assessment.

Overall, the included reviews found well-conducted studies showing an association between preterm birth and particulate matter and ozone including a high number of studies from Europe and North America. Even if there are still contrary results and a lack of co-pollutant models, there was little detected publication bias. The epidemiologic evidence is still limited, but taking evidence from toxicological studies into account, the relationship is *suggestive* according to the US EPA ISA on ozone and PM. However, a relationship between preterm birth and other pollutants is inconclusive and according to the US EPA ISA on PM the biological mechanisms playing a role are still uncertain. This is in line with the WHO reporting a growing evidence between preterm birth and air pollution, especially for PM (2018). Thus, the evidence for an association between preterm birth and particulate matter and ozone can be considered as moderate.

**Table 17: Results of the included reviews on preterm birth attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | pollutant(s) (focus) | Selected results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| PTB and subtypes | Yu (2022) | PM: $PM_{10}$, $PM_{2.5}$, PM1, UFP | Preterm birth was consistently associated with $PM_{2.5}$ and $PM_{10}$ exposure during entire pregnancy, as well as with $PM_{2.5}$ exposure in the second and third trimester. | moderate | (98) |
| PTB | Nyadanu (2022) | $PM_{2.5}$, $PM_{10}$, $NO_2$, CO | Less consistent evidence for an association between preterm birth and AP | per pollutant (e.g. less consistent) | (97) |
| PTB | HEI (2022) | TRAP: $NO_2$, NO, NOx, BC/EC, $PM_{2.5}$, $PM_{10}$, CO | Low evidence for an association between TRAP and preterm birth | low | (99) |
| PTB | US EPA (2010) | CO | There was limited evidence that CO during first and second trimester was associated with PTB | limited | (32) |
| LT: PTB | US EPA (2020) | Ozone | The epidemiologic evidence is still limited, but taking evidence from toxicological studies into account, the relationship is *suggestive* | suggestive | (23) |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 18: Characteristics of included reviews on preterm birth attributed to ambient air pollution**

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search up to | DB searched | Publication year range | Origin of studies | RoB tool |
|---|---|---|---|---|---|---|---|---|---|
| PTB and subtypes | Yu (2022) | PM: $PM_{10}$, $PM_{2.5}$, PM1, UFP | yes | 84 (LT:77, | Mar 2022 | 4 | 2000-2021 | Asia (35), North America (29), Australia (5), Europe (9), Iran (3), South America (3) | Navigation guide OHAT, NOS, GRADE |
| PTB | Nyadanu (2022) | $PM_{2.5}$, $PM_{10}$, $NO_2$, CO | yes | 36 reviews (21 with meta):295 primary studies | Mar 2022 | 6 | NR | overall: North America (125), Europe (52), Asia (70), other (48) | yes JBI |
| PTB | HEI (2022) | TRAP: $NO_2$, NO, NOx, BC/EC, $PM_{2.5}$, $PM_{10}$, CO | yes | 30 | Jul 2019 | 2 | 2002-2019 | Europe (10), North America (11), Asia | OHAT and narrative |
| PTB | US EPA (2010) | CO | no | 7 | May 2009 | HERO database | NR | | yes |
| PTB | US EPA (2020) | Ozone | no | 29 | Mar 2018 | HERO database | NR | | yes |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 19: Summary estimates from meta-analyses from selected reviews on preterm birth attributed to ambient air pollution**

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric [HR, OR, RR] | Estimate | 95%-CI | Model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PTB | $PM_{2.5}$ entire pregnancy* | Yu (2022) | 10 µg/m³ | 43 | RR | **1.084** | **1.055-1.113** | RE | 0.989 | <0.001 | no indication of publication bias |
| PTB | $PM_{2.5}$ second trimester | Yu (2022) | 10 µg/m³ | 38 | RR | **1.021** | **1.001-1.041** | RE | 0.939 | <0.001 | no indication of publication bias |
| PTB | $PM_{2.5}$ third trimester | Yu (2022) | 10 µg/m³ | 31 | RR | **1.02** | **1.008-1.033** | RE | 0.971 | <0.001 | no indication of publication bias |
| PTB | $PM_{10}$ entire pregnancy | Yu (2022) | 10 µg/m³ | 21 | RR | **1.034** | **1.018-1.049** | RE | 0.839 | <0.001 | detected, trim and fill strengthened results |
| PTB | $NO_2$ entire pregnancy | HEI (2022) | 10 µg/m³ | 14 | RR | 1.00 | 0.96-1.04 | RE | 0.79 | <0.1 | no indication of publication bias |
| PTB | NOx entire pregnancy | HEI (2022) | 22 µg/m³ | 6 | RR | 1.03 | 0.90-1.17 | RE | 0.85 | <0.1 | too few studies |
| PTB | EC entire pregnancy | HEI (2022) | 1 µg/m³ | 5 | RR | 1.02 | 0.97-1.07 | RE | 0.56 | 0.06 | too few studies |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

*Reading example for the association of preterm birth with $PM_{2.5}$ exposure: (Yu 2022): the PTB risk was **significantly** increased by 8%, with a confidence range of the true effect between 5.5 and 11% for a 10 µg/m³ higher $PM_{2.5}$ exposure over the whole pregnancy period. Heterogeneity $I^2$ of study results was high, indicating a high between study variation. Publication bias was not detected. Statistical significance (indicated as bold effect estimates) refers to the probability that the observed result could have occurred randomly if it has no true underlying effect. If an estimate is significant, such random occurence is unlikely.

### Birth Weight

Two reviews by Ghosh et al. (100) and by Yang et al. (101) and one umbrella review by Nyadanu et al. (97) were included, as well as the integrated science assessment of the US EPA for ozone (see Table 20 to Table 22 below). Ghosh et al. (100) investigated the association between birth weight and $PM_{2.5}$ and found 44 studies published between 2005 and 2020. Yang et al. (101) investigated effects of PAHs and included 12 studies published between 1998-2017. Both reviews conducted a meta-analysis and assessed the level of evidence. Nyadanu et al. (97) included 36 reviews on birth outcomes and particulate matter, carbon monoxide, ozone, $SO_2$ and $NOx/NO_2$, seven of them on birth weight and used the JBI critical appraisal tool to assess the evidence. The US EPA ISA on ozone (23) included 7 new studies since the US EPA ISA on ozone from 2010, searched until march 2018, adding up to 19 studies. Since there were no recent reviews on benzene the review by Protano et al. (102) was added to the analysis as well. They found only 3 studies published between 2003 and 2011. Additionally for TRAP, we also included the HEI report (99) that examined 18 studies. As supporting evidence we also included the US EPA ISAs on PM (17) and $NO_2$ (25).

Overall, the most consistent association was found between continuous birth weight and $PM_{2.5}$ without indication of publication bias. However, heterogeneity was high. Without the inclusion of other studies, such as toxicological studies with animals, the evidence for a relationship between birth weight and exposure to $PM_{10}$, $NO_2$ and Ozone was less consistent positive. However, when possible biological pathways are included, the evidence might be *suggestive* for PM and ozone. Additionally, these results are strengthened by the findings of the HEI report, which found moderate evidence for traffic-specific $PM_{2.5}$. Most reviews included a high number of studies from Europe and North America. We consider the evidence for continuous birthweight as moderate for particulate matter and suggestive for ozone.

**Table 20: Results of the included reviews on birth weight attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant(s) (focus) | Selected results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| Birth weight | Nyadanu (2022) | PMs, $NO_2$, $O_3$, $SO_2$, CO | Rather consistent evidence for an association between birth weight and $PM_{2.5}$ during the entire pregnancy, some associations with $NO_2$ and $PM_{2.5}$. Unclear or conflicting evidence for ozone, $SO_2$ and CO | NR | (97) |
| Term birth weight | HEI (2022) | TRAP: $NO_2$, NO, NOx, BC/EC, $PM_{2.5}$, $PM_{10}$, CO | Low evidence for $PM_{2.5}$ in traffic studies and low evidence for Nox, $NO_2$ and EC | low | (99) |
| Birth weight | Ghosh (2021) | $PM_{2.5}$ | Significantly lower birth weight was associated with $PM_{2.5}$ | strong | (100) |
| Birth weight | Yang (2020) | PAH | Based on few studies there was no association between PAHs and birth weight | NR | (101) |
| BW, PTB | Protano (2012) | Benzene | Conflicting effect estimates from very few studies | NR | (102) |
| Birth weight | US EPA (2010) | CO | According to most studies birth weight was associated with CO exposure, especially in the first and third trimester | limited | (32) |
| LT: birth outcomes | US EPA (2020) | Ozone | Some evidence from epidemiological and toxicological studies for an association. Taken together, the evidence was rated as suggestive. | suggestive | (23) |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 21: Characteristics of included reviews on birth weight attributed to ambient air pollution**

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search date up to | DB searched | Publication year range | Origin of studies (#) | Quality tool |
|---|---|---|---|---|---|---|---|---|---|
| Birth weight | Nyadanu (2022) | CO | Various reviews | various | Mar 2022 | 6 | NR | overall: North America (125), Europe (52), Asia (70), other (48) | JBI |
| Term birth weight | HEI (2022) | TRAP: $NO_2$, NO, NOx, BC/EC, $PM_{2.5}$, $PM_{10}$, CO | yes | 15 | Jul 2019 | 2 | 2010-2017 | Europe, North America | OHAT and narrative |
| Birth weight | Ghosh (2021) | $PM_{2.5}$ | yes | 44 | Apr 2021 | 3 | 2005-2020 | Europe (11), North America (38), Asia (10), other (5) | Checklists and NIEHS |
| Birth weight | Yang (2020) | PAH | yes | 12 | May 2020 | 4 | 1998-2017 | Europe (4), North America (3), Asia (4), other (1) | Lam |
| BW, PTB | Protano (2012) | Benzene | no | 6: BW 3, PTB 1 | Apr 2011 | 3 | 2003-2011 | Europe | yes |
| Birth weight | US EPA (2010) | CO | no | 15 | May 2009 | HERO database | NR | global | yes |
| LT: birth outcomes | US EPA (2020) | Ozone | no | 19 | Mar 2018 | HERO database | NR | global | yes |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 22: Summary estimates from meta-analyses from selected reviews on birth weight attributed to ambient air pollution**

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric [HR, OR, RR] | Estimate | 95%-CI | Model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Term birth weight | $NO_2$ | HEI (2022) | 10 µg/m$^3$ | 8 | grams | -3.2 | -11.0;4.6 | RE | 0.97 | <0.01 | too few studies |
| Term birth weight | NOx | HEI (2022) | 20 µg/m$^3$ | 5 | grams | -3.4 | -11.7;4.8 | RE | 0.97 | <0.01 | too few studies |
| Term birth weight | EC | HEI (2022) | 1 µg/m$^3$ | 4 | grams | -2.6 | -6.1; 0.9 | RE | 0 | 0.41 | too few studies |
| Term birth weight | $PM_{2.5}$ | HEI (2022) | 10 µg/m$^3$ | 6 | grams | **-17.3** | **(-33.5; -1.5)** | RE | 99.09 | <0.01 | too few studies |
| Birth weight | $PM_{2.5}$* | Ghosh (2021) | 10 µg/m$^3$ | 44 | grams | **-22** | **(-12; -32)** | maximum likelihood method | >99% | NR | no indication of publication bias |
| Birth weight (restricing to studies including term and preterm births) | $PM_{2.5}$ | Ghosh (2021) | 10 µg/m$^3$ | 13 | grams | **-35** | **(-15; -55)** | maximum likelihood method | >99% | NR | no indication of publication bias |
| Term birth weight | PAH | Yang (2020) | 1 ln ng/m3 | 4 | OR | 0.97 | 0.93, 1.01 | RE | 87% | <0.001 | detected |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

*Reading example for the association of birth weight with $PM_{2.5}$ exposure: (Ghosh 2021): the birth weight is **significantly** reduced by 22g, with a confidence range of the true effect between 12 and 32 gramms for a 10 µg/m$^3$ higher $PM_{2.5}$ exposure over the whole pregnancy period. Heterogeneity $I^2$ of study results was high, indicating a high between study variation. Publication bias was not detected. Statistical significance (indicated as bold effect estimates) refers to the probability that the observed result could have occurred randomly if it has no true underlying effect. If an estimate is significant, such random occurrence is unlikely.

### Small for gestational age

Two reviews with a meta-analysis (99,103) and one umbrella review (97) were included (see Table 23 to Table 25 below). Pun et al. (103) found 49 studies on ambient particulate matter and 17 studies on indoor air pollution and cooking published between 1990-2020. Risk of bias (RoB) and level of evidence was not assessed. In contrast, the HEI report (99) on traffic-related air pollution (TRAP) conducted a thorough RoB according to OHAT and included 25 studies on small for gestational age. Nyadanu et al. (97) included 36 reviews on birth outcomes and air pollution, two of them on SGA and $PM_{2.5}$. JBI critical appraisal tool was used to assess the evidence.

Overall, SGA is less frequently studied than preterm birth or low birth weight. There is rather consistent evidence that an increased risk might be associated with SGA based on a number of studies from Europe and North America. However, the number of well-designed studies is low and the heterogeneity between studies high. The HEI report (99) considered the evidence for traffic-related $PM_{2.5}$ as *low* and for $PM_{10}$ as *moderate*. Taking into account the narrative assessment, the overall evidence for TRAP was assessed as *moderate*. Thus, the evidence for an association between SGA and air pollution can be considered as moderate.

**Table 23: Results of the included reviews on small for gestational age attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant(s) (focus) | Selected results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| SGA | Nyadanu (2022) | $PM_{2.5}$ | Significantly elevated risk for SGA, however, overall evidence seemed to be a less consistent positive *association* for the entire pregnancy period | Less consistent positive | (97) |
| Small for gestational age SGA | HEI (2022) | TRAP: $NO_2$, NO, NOx, BC/EC, $PM_{2.5}$, $PM_{10}$, CO | Overall confidence in body of evidence was moderate, however, the evidence for $PM_{2.5}$ was low due to the modest amount of large birth cohort studies and moderate for $PM_{10}$. Furthermore, the confidence for the null findings for $NO_2$ were also rated as moderate. | moderate | (99) |
| Stunting (too small for age) | Pun (2021) | PMs, cooking/ indoor air | Increased risk for SGA associated with $PM_{2.5}$ in the entire pregnancy and second and thrid trimester | NR | (103) |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 24: Characteristics of included reviews on small for gestational age attributed to ambient air pollution**

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search up to | DB searched | Publication year range | Origin of studies | Quality tool |
|---|---|---|---|---|---|---|---|---|---|
| SGA | Nyadanu (2022) | $PM_{2.5}$ | 2 reviews | 36 reviews (21 with meta): 295 primary studies | Mar 2022 | 6 | | overall: North America (125), Europe (52), Asia (70), other (48) | JBI |
| Small for gestational age SGA | HEI (2022) | TRAP: $NO_2$, NO, NOx, BC/EC, $PM_{2.5}$, $PM_{10}$, CO | yes | 25 | Jul 2019 | 2 | 2008-2018 | Europe (9), North America, Asia | OHAT and narrative |
| Stunting (too small for age) | Pun (2021) | PMs, cooking/indoor air | yes | 66 (49 ambient air-43 in metaanalysis) | Aug 2020 | 4 | 1999-2020 | Europe (2) and other countries | none |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 25: Summary estimates from meta-analyses from selected reviews on small for gestational age attributed to ambient air pollution**

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric [HR, OR, RR] | Estimate | 95%-CI | Model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| SGA | TRAP: $PM_{2.5}$ entire pregnancy | HEI (2022) | 5 µg/m³ | 4 | OR | **1.09** | **1.04-1.14** | RE | 0 | 0.76 | too few studies |
| SGA | $PM_{10}$ entire pregnancy | HEI (2022) | 5 µg/m³ | 4 | OR | **1.08** | **1.01-1.14** | RE | 0.11 | 0.34 | too few studies |
| SGA | $NO_2$ entire pregnancy | HEI (2022) | 10 µg/m³ | 11 | OR | 1.00 | 0.96-1.04 | RE | 0.45 | 0.05 | no indication of publication bias |
| SGA | EC entire pregnancy | HEI (2022) | 1 µg/m³ | 3 | OR | 1.03 | 0.92-1.14 | RE | 0.47 | 0.15 | too few studies |
| SGA | $PM_{2.5}$ entire pregnancy* | Pun (2021) | 10 µg/m³ | 11 | OR | **1.08** | **1.03-1.13** | RE | 0.92 | <0.01 | no indication of publication bias |
| SGA | $PM_{2.5}$ second trimester | Pun (2021) | 10 µg/m³ | 10 | OR | **1.04** | **1.02-1.06** | RE | 0.78 | <0.01 | no indication of publication bias |
| SGA | $PM_{2.5}$ third trimester | Pun (2021) | 10 µg/m³ | 10 | OR | **1.05** | **1.00-1.09** | RE | 0.91 | <0.01 | detected |
| SGA | $PM_{10}$ entire pregnancy | Pun (2021) | 10 µg/m³ | 12 | OR | **1.03** | **1.00-1.05** | RE | 0.87 | 0.0361 | no indication of publication bias |
| SGA | $PM_{10}$ first trimester | Pun (2021) | 10 µg/m³ | 11 | OR | **1.01** | **1.00-1.13** | RE | 0.85 | 0.1059 | no indication of publication bias |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

*Reading example for the association of SGA with $PM_{2.5}$ exposure: (Pun 2021): the SGA risk was **significantly** increased by 8%, with a confidence range of the true effect between 1 and 14% for a 10 µg/m³ higher $PM_{2.5}$ exposure over the whole pregnancy period. Heterogeneity $I^2$ of study results was high, indicating a high between study variation. Publication bias was not detected. Statistical significance (indicated as bold effect estimates) refers to the probability that the observed result could have occurred randomly if it has no true underlying effect. If an estimate is significant, such random occurrence is unlikely.

### (Term) Low birth weight

One review by Ghosh et al. (100), the HEI TRAP report (99) and one umbrella review by Nyadanu et al. (97) were included (see Table 26 to Table 28 below). Ghosh et al. (100) investigated the association between low birth weight, a birth weight smaller than 2500g, and $PM_{2.5}$ and found 40 studies published between 2005 and 2020. Nine studies included all births not only term births. The association between term low birth weight and traffic-related $PM_{2.5}$, $PM_{10}$, $NO_2$, NOx and EC was investigated in the HEI report (99). They found 25 studies published between 2003 and 2019. Nyadanu et al. (97) included 36 reviews on birth outcomes and particulate matter, carbon monoxide, ozone, $SO_2$ and $NOx/NO_2$, seven of them on low birth weight. All articles conducted a meta-analysis and assessed the level of evidence.

There is strong evidence for an association between low birth weight and $PM_{2.5}$ and $SO_2$, and moderate evidence for traffic-specific $PM_{2.5}$, NOx and EC. The HEI report found for $PM_{2.5}$ some evidence for a monotonic dose-response function. Those ratings are in line with a WHO report from 2018 that found *strong* evidence for an association of air pollution with low birth weight. The reviews draw evidence from a number of European and North America n studies. We therefore see moderate to strong evidence for harmful effects of air pollution regarding the risk of low birth weight.

**Table 26: Results of the included reviews on low birth weight attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant(s) (focus) | Selected results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| Term low birth weight | HEI (2022) | TRAP: $NO_2$, NO, NOx, BC/EC, $PM_{2.5}$, $PM_{10}$, CO | Moderate evidence for an association between long-term Nox, EC and $PM_{2.5}$ and low evidence for $PM_{10}$ and very low for CO and term low birth weight | moderate | (99) |
| Low birth weight | Ghosh (2021) | $PM_{2.5}$ | Greater risk of low birth weight was consistently associated with $PM_{2.5}$ | strong evidence $PM_{2.5}$ | (100) |
| Low birth weight | Nyadanu (2022) | $NO_2$, CO, $O_3$, $SO_2$,$PM_{2.5}$, and $PM_{10}$ | Rather consistent association for $PM_{2.5}$, less consistent for $PM_{10}$ and $NO_2$, unclear associations for ozone and $SO_2$ | | (97) |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 27: Characteristics of included reviews on low birth weight attributed to ambient air pollution**

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search up to | DB searched | Publication year range | Origin of studies | RoB tool |
|---|---|---|---|---|---|---|---|---|---|
| Term low birth weight | HEI (2022) | TRAP: $NO_2$, NO, NOx, BC/EC, $PM_{2.5}$, $PM_{10}$, CO | yes | 25 | Jul 2019 | 2 | 2003-2019 | Europe (10), North America (10), South America, Asia | OHAT and narrative |
| Low birth weight | Ghosh (2021) | $PM_{2.5}$ | yes | 40 | Apr 2021 | 3 | 2007-2021 | Europe (11), North America (38), Asia (10), other (5) | Checklists and NIEHS |
| Low birth weight | Nyadanu (2022) | $NO_2$, CO, $O_3$, $SO_2$,$PM_{2.5}$, and $PM_{10}$ | | 36 reviews (21 with meta):295 primary studies | Mar 2022 | 6 | NR | overall: North America (125), Europe (52), Asia (70), other (48) | yes JBI |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 28: Summary estimates from meta-analyses from selected reviews on low birth weight attributed to ambient air pollution**

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric [HR, OR, RR] | Estimate | 95%-CI | Model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Term low birth weight | $PM_{2.5}$ entire pregnancy | HEI (2022) | 5 µg/m$^3$ | 7 | RR | **1.11** | **1.03-1.20** | RE | 0.84 | <0.01 | too few studies |
| Term low birth weight | $PM_{10}$ entire pregnancy | HEI (2022) | 10 µg/m$^3$ | 3 | RR | 1.14 | 0.95-1.38 | RE | 0 | 0.45 | too few studies |
| Term low birth weight | CO entire pregnancy | HEI (2022) | 1 mg/m3 | 3 | RR | 1.06 | 0.67-1.68 | RE | 0.52 | 0.13 | too few studies |
| Term low birth weight | $NO_2$ entire pregnancy | HEI (2022) | 10 µg/m$^3$ | 12 | RR | 1.01 | 0.99-1.03 | RE | 0.71 | <0.01 | no indication of publication bias |
| Term low birth weight | NOx entire pregnancy | HEI (2022) | 20 µg/m$^3$ | 5 | RR | **1.02** | **1.01-1.02** | RE | 0 | 0.75 | too few studies |
| Term low birth weight | NOx third trimester | HEI (2022) | 20 µg/m$^3$ | 5 | RR | **1.01** | **1.01-1.02** | NR | NR | NR | too few studies |
| Term low birth weight | EC second trimester | HEI (2022) | 20 µg/m$^3$ | 5 | RR | **1.02** | **1.01-1.04** | NR | NR | NR | too few studies |
| Term low birth weight | EC third trimester | HEI (2022) | 20 µg/m$^3$ | 5 | RR | **1.03** | **1.03-1.04** | NR | NR | NR | too few studies |
| Low birth weight | $PM_{2.5}$ entire pregnancy | Ghosh (2021) | 10 µg/m$^3$ | 40 | RR | **1.11** | **1.07-1.16** | maximum likelihood method | 0.95 | NR | detected |
| Low birth weight | $SO_2$ entire pregnancy | Nyadanu (2022) | 10 ppb | 1 review | RR | **1.12** | **1.02-1.24** | NR | 0.83 | NR | NR |
| Low birth weight | $SO_2$ entire pregnancy | Nyadanu (2022) | 10 ppb | 1 review | RR | 1.06 | 1.04-1.10 | NR | 0 | NR | NR |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

* Reading example for the association of low birth weight with $PM_{2.5}$ exposure: (Ghosh 2021): the risk to be born with a low birth weight was **significantly** increased by 11%, with a confidence range of the true effect between 7 and 16% for a 10 µg/m$^3$ higher $PM_{2.5}$ exposure over the whole pregnancy period. Heterogeneity $I^2$ of study results was high, indicating a high between study variation. There was an indication of publication bias. Statistical significance (indicated as bold effect estimates) refers to the probability that the observed result could have occurred randomly if it has no true underlying effect. If an estimate is significant, such random occurrence is unlikely.

### Intrauterine growth restriction

One review by Fu et al. (104) was included (see Table 29 to Table 31 below). They investigated the association between intrauterine growth restriction measured by ultrasound and anthropometric indicators at birth such as head circumference and exposure to $PM_{10}$, $PM_{2.5}$, $NO_2$, NOx, $SO_2$, carbon monoxide and ozone. 15 studies published between 2007 and 2017 were included. The majority of studies were conducted on Europe or North America. Meta-analysis and RoB assessment was conducted for $PM_{2.5}$, $PM_{10}$ and $NO_2$. Body of evidence was evaluated with GRADE.

There are studies showing that exposure to higher $NO_2$ and $PM_{2.5}$ levels might reduce head circumference and birth length. However, the effects of air pollutants on intrauterine growth remain inconclusive due to the general low number of studies and the rather low methodological quality of studies. Also, intrauterine growth restriction is not listed in the UN publications on children's health (19,21,105). We consider the evidence as low.

**Table 29: Results of the included reviews on intrauterine growth restriction attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant(s) (focus) | Selected results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| Intrauterine growth restriction (ultrasound (HC, AC,BPD, FL, and length) and anthropometric measurements (HC, AC, and length) at birth) | Fu (2019) | $NO_2$, $PM_{10}$, $PM_{2.5}$, NOX, $SO_2$, $O_3$, CO | Maternal exposure to higher $NO_2$ and $PM_{2.5}$ during pregnancy was associated with neonatal head circumference and length development. | inconclusive | (104) |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 30: Characteristics of included reviews on intrauterine growth restriction attributed to ambient air pollution**

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search up to | DB searched | Publication year range | Origin of studies | Quality tool |
|---|---|---|---|---|---|---|---|---|---|
| Intrauterine growth restriction (ultrasound (HC, AC,BPD, FL, and length) and anthropometric measurements (HC, AC, and length) at birth) | Fu (2019) | $NO_2$, $PM_{10}$, $PM_{2.5}$, NOX, $SO_2$, $O_3$, CO | yes | 15 | Jul 2017 | 5 | 2007-2017 | Europe (12), North America (1), Australia (2) | ACROBAT-NRSI, GRADE |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 31: Summary estimates from meta-analyses from selected reviews on intrauterine growth restriction attributed to ambient air pollution**

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric [HR, OR, RR] | Estimate | 95%-CI | Model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| fetal and birth head circumference | $NO_2$ entire pregnancy | Fu (2019) | 10 µg/m$^3$ | 8 | beta | -0.02 | (-0.06, 0.01) | RE | 94.75% | NR | not detected |
| fetal and birth head circumference | $PM_{10}$ entire pregnancy | Fu (2019) | 10 µg/m$^3$ | 3 | beta | -0.13 | (-0.25, 0.00) | RE | 96.75% | NR | not detected |
| fetal and birth head circumference | $PM_{2.5}$ entire pregnancy* | Fu (2019) | 10 µg/m$^3$ | 3 | beta | **-0.3** | **(-0.49, -0.10)** | RE | 73.48% | NR | not detected |
| birth length | $NO_2$ entire pregnancy | Fu (2019) | 10 µg/m$^3$ | 4 | beta | **-0.03** | **(-0.05, -0.02)** | RE | 0.00% | NR | not detected |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

*Reading example for the association of fetal and birth head circumference with $PM_{2.5}$ exposure: (Ghosh 2021): the head circumference was **significantly** reduced by 0.3 cm, with a confidence range of the true effect between 0.1 and 0.49 cm for a 10 µg/m$^3$ higher $PM_{2.5}$ exposure over the whole pregnancy period. Heterogeneity $I^2$ of study results was high, indicating a high between study variation and publication bias was not detected. Statistical significance (indicated as bold effect estimates) refers to the probability that the observed result could have occurred randomly if it has no true underlying effect. If an estimate is significant, such random occurrence is unlikely.

### Congenital anomalies

Two reviews for congenital heart diseases (106,107), the US EPA ISA on ozone (23) and carbon monoxide (32), as well as two reviews for orofacial defects and other anomalies (107,108) and two reviews for hypospadias (109,110) were included (see Table 32 to Table 34 below). Xing et al. (109) investigated the association between hypospadias and the exposure to particulate matter, $NO_2$, ozone, $SO_2$ and carbon monoxide. They found 16 studies published between 1998-2020 and conducted a RoB assessment with OHAT and a meta-analysis. We also included Lin et al. (110) since they report other results based on the same studies in the meta-analysis. Evidence was not assessed in both studies. Ma et al. (106) investigated the association between congenital heart disease and particulate matter, $NO_2$, $SO_2$, carbon monoxide and ozone. They found 24 studies published between 2002 and 2019. A meta-analysis was conducted, but the quality of the body of evidence was not examined. Ravindra et al. (107) examined various congenital anomalies, including congenital heart diseases and included 26 studies published between 2009 and 2018. They also did a meta-analysis and used ROBINS-E to evaluate risk of bias and the evidence. Furthermore the US EPA ISA for CO (32) included 5 studies and the ISA for ozone 12 studies since the last report 2013. Rao et al. (108) investigated the association between orofacial clefts and particulate matter, SO2, NO2, carbon monoxide and ozone in 8 studies published between 2000 and 2012. A meta-analysis was conducted and risk of bias was assessed, but not the level of evidence. The newer review by Ravindra et al. (107) additionally examined the relationship between AP and multiple congenital anomalies (orofacial clefts, limb defects, nervous system anomalies and other congenital anomalies). The majority of included studies were conducted on Europe or North America.

Overall, very few studies have examined the association between hypospadias and air pollution. There is *insufficient evidence* to determine a relationship. Similar to hypospadias, there is *very limited evidence* for a relationship between air pollution and orofacial clefts. The most suggestive evidence was found for ozone. However, there is no supporting evidence from experimental animal studies according to the US EPA ISA for ozone. The risk of limb and neurological defects have rarely been studied in epidemiological studies. There is some evidence that maternal exposure to air pollution is associated with an increased risk of congenital heart diseases, which is partly supported by some animal toxicological studies. This would also be coherent with the evidence on CVD effects from CO. However, there are contradictory results and no consistent linear or dose-response relationships between malformations and any air pollutant are reported. Further studies are needed to clarify such associations. The evidence for a relationship between malformations and air pollution altogether is very low. Additionally, none of the UN-reports has mentioned this outcome. Therefore, the evidence for an association between malformations and AP can be considered as low.

**Table 32: Results of the included reviews on malformations attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant(s) (focus) | Selected results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| Hypospadias | Xing (2021) | NOS, PMS, $O_3$, $SO_2$, CO | PM(2.5) exposure in the first trimester was related to increased risk of hypospadias | NR | (109) |
| Congenital anomalies | Ravindra (2021) | $SO_2$, $NO_2$, NOx, $PM_{2.5}$, $PM_{10}$, $O_3$, CO,BC | Associations were found for nitrogen dioxide or PM(2.5) with the risk of pulmonary valve stenosis, the risk of developing tetralogy of Fallot (TOF). | low | (107) |
| Congenital Heart Disease | Ma (2021) | PMs, $SO_2$, $NO_2$, CO, $O_3$ | Associations between the different congenital heart disease subtypes and AP, but not in the overall analysis. | NR | (106) |
| Hypospadias | Lin (2021) | $PM_{2.5}$, $PM_{10}$, $PM_{10\text{-}2.5}$ | The risk for hypospadias was increased for $PM_{2.5}$ during the frist trimester as well as 1 month before pregnancy. | NR | (110) |
| Orofacial Clefts | Rao (2016) | $PM_{10}$, $SO_2$, O2, $NO_2$, CO, NOx | Risk of orofacial cleft anomalies associated with ozone, risk of cleft lip with or without palate cleft palate with NOx. | $O_3$. Strongest correlation, overall inconsistent | (108) |
| Congenital anomalies | US EPA (2010) | CO | there is some evidence that maternal exposure to CO is associated with an increased risk of congenital anomalies, namely heart defects and cleft lip and palate. | some evidence | (32) |
| Malformations | US EPA (2010) | CO | Maternal CO exposure was associated with an increased risk of cardiac birth defects, which is also coherent with evidence in Section 5.2 identifying the heart as a target organ for CO. | suggestive | (32) |
| birth defects (cardiac defects) | US EPA (2020) | Ozone | Ozone-associated birth defects are generally inconsistent across epidemiologic studies, and there are no experimental animal studies on birth defects. | unclear/inconsistent | (23) |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 33: Characteristics of included reviews on malformations attributed to ambient air pollution**

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search up to | DB searched | Publication year range | Origin of studies | Quality tool |
|---|---|---|---|---|---|---|---|---|---|
| Hypospadias | Xing (2021) | NOS, PMS, $O_3$, $SO_2$, CO | yes | 16 | Jan 2020 | 2 | 1998-2020 | Europe (8), North America (6), Asia (2) | OHAT |
| Congenital anomalies | Ravindra (2021) | $SO_2$, $NO_2$, NOx, $PM_{2.5}$, $PM_{10}$, $O_3$, CO,BC | yes | 26 | 1950-Aug 2019 | 2 | 2009-2018 | Europe (8), North America (10), Asia (4) | ROBINS-E, GRADE |
| Congenital Heart Disease | Ma (2021) | PMs, $SO_2$, $NO_2$, CO, $O_3$ | yes | 24 | Jul 2020 | 3 | 2002-2019 | Europe (7), North America (8), Asia (6) other (3) | NOS |
| Hypospadias | Lin (2021) | $PM_{2.5}$, $PM_{10}$, $PM_{10-2.5}$ | yes $PM_{2.5}$ | 9 | Feb 2020 | 2 | 2013-2020 | Europe (4), North America (4), Asia (1) | NOS |
| Orofacial Clefts | Rao (2016) | $PM_{10}$, $SO_2$, O2, $NO_2$, CO, Nox | yes | 8 | Jan 1980-Dec 2012 | yes | 2002-2012 | North America (3), Europe (2), Asia (2) other (1) | Antczak et al. and Jadad et al. were utilized. |
| Congenital anomalies | US EPA (2010) | CO | no | 5 | May 2009 | HERO database | 2002-2009 | - | yes |
| Malformations | US EPA (2010) | CO | no | NR | May 2009 | HERO database | NR | - | yes |
| Birth defects (cardiac defects) | US EPA (2020) | Ozone | no | 12 | Mar 2018 | HERO database | 2011-2016 | - | yes |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure

**Table 34: Summary estimates from meta-analyses from selected reviews on malformations attributed to ambient air pollution**

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric [HR, OR, RR] | Estimate | 95%-CI | Model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hypospadias | first trimester $PM_{2.5}$ | Xing (2021) | 10 µg/m³ | 5 | OR | **1.34** | **1.06-1.68** | RE | 0.547 | 0.039 | no indication of publication bias |
| Hypospadias | first trimester ozone | Xing (2021) | 5 ppb | 4 | OR | 1.03 | 0.96-1.11 | RE | 0.535 | 0.117 | detected, not discussed |
| pulmonary valve stenosis | $PM_{2.5}$ | Ravindra (2021) | 5 µg/m³ | 3 | OR | **1.42** | **1.36-1.48** | RE | 0.984 | <0.001 | undetected |
| Tetralogy of Fallot | $PM_{2.5}$ | Ravindra (2021) | 5 µg/m³ | 3 | OR | **1.52** | **1.44-1.60** | RE | 0.976 | <0.001 | undetected |
| limb defects | $PM_{2.5}$ | Ravindra (2021) | 5 µg/m³ | 4 | OR | 0.76 | 0.72-0.80 | RE | significant | <0.001 | undetected |
| neural tube defects | $PM_{2.5}$ | Ravindra (2021) | 5 µg/m³ | 3 | OR | 0.87 | 0.75-0.98 | RE | significant | <0.001 | undetected |
| orofacial clefts | $PM_{10}$ | Ravindra (2021) | 10 µg/m³ | 3 | OR | 0.87 | 0.79-0.93 | RE | significant | <0.001 | undetected |
| limb defects | $PM_{10}$ | Ravindra (2021) | 10 µg/m³ | 4 | OR | 0.83 | 0.80-0.86 | RE | significant | <0.001 | undetected |
| pulmonary valve stenosis | $NO_2$* | Ravindra (2021) | 10 ppb | 3 | OR | **1.74** | **1.68-1.81** | RE | 0.981 | <0.001 | undetected |
| atrium septal defects | $SO_2$ | Ravindra (2021) | 1 µg/m³ | 3 | OR | 0.87 | 0.86-0.87 | RE | significant | <0.001 | undetected |
| ventricular septal defect | $SO_2$ | Ravindra (2021) | 1 µg/m³ | 4 | OR | **1.15** | **1.10-1.20** | RE | 0.957 | <0.001 | undetected |

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric [HR, OR, RR] | Estimate | 95%-CI | Model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ventricular septal defect | $PM_{2.5}$ (developing countries) | Ma (2021) | NR | NR | RR | **1.208** | **1.080-1.337** | RE | high | NR | no indication of publication bias |
| ventricular septal defect | $PM_{2.5}$ (exposure ass. within 3-8 weeks) | Ma (2021) | NR | NR | RR | **1.057** | **1.005-1.109** | RE | high | NR | no indication of publication bias |
| ventricular septal defect | ozone (developing countries) | Ma (2021) | NR | NR | RR | **1.205** | **1.101-1.310** | RE | high | NR | no indication of publication bias |
| Hypospadias | first trimester $PM_{2.5}$ | Lin (2021) | IQR | 5 | OR | **1.17** | **1.00-1.36** | RE | 0.568 | 0.055 | detected, trim and fill attenuated results to ns |
| cleft palate only | NOx | Rao (2016) | NR | 4 | OR | 0.84 | 0.71-1.00 | FE | NR | NR | NR |
| cleft palate only | CO | Rao (2016) | NR | 4 | OR | 0.88 | 0.78-0.99 | FE | NR | NR | NR |
| cleft lip with or without palate | Ozone | Rao (2016) | NR | 4 | OR | **1.08** | **1.01-1.16** | FE | NR | NR | NR |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

*Reading example for the association of pulmonary valve stenosis risk with $NO_2$ exposure: (Ravindra 2021): the risk to be born with pulmonary valve stenosis was **significantly** increased by 74%, with a confidence range of the true effect between 68 and 81% for a 10 ppb higher $NO_2$ exposure. Heterogeneity $I^2$ of study results was high, indicating a high between study variation. Publication bias was not detected. publication bias was not detected. Statistical significance (indicated as bold effect estimates) refers to the probability that the observed result could have occurred randomly if it has no true underlying effect. If an estimate is significant, such random occurrence is unlikely.

### *Respiratory effects*

#### Infections

Eight reviews and the US EPA ISAs for PM, ozone, $NO_2$ and $SO_2$ were selected (see Table 35 to Table 37 below). The reviews reported on associations of air pollution with acute lower respiratory infections (ALRI) (99,111,112) or diagnoses within that definition like pneumonia (113) or bronchiolitis King et al. (114), otitis media (115,116), and upper respiratory tract infections (117). Evidence from these reviews was supported by the integrated sciences assessments. The reviews were of high quality using the Newcastle-Ottawa Scale or the OHAT methodology for study quality assessment, except for the reviews by Nhung et al. (113), Mehta et al. (111) and Låg et al (112) that searched only one database and did not assess study quality.

The HEI review (99) included 27 studies published between 1995 and 2019 on ALRI and provided pooled results for NO2 and EC as markers of TRAP. Mehta et al (111) provided pooled effect estimates for the association of ALRI with long-term $PM_{2.5}$ from 4 studies published 2002-2009. As a subcategory of ALRI King et al. (114) studied bronchiolitis in children with various pollutants. The eight studies were published 2004-2017. Due to the low number of studies meta-analysis was not attempted. Short-term effects of air pollutants on pneumonia in children were analyzed in Nhung et al. (113), including 17 studies published between 1999-2016.

Otitis media risk with short- and long-term PM exposure was studied in Lee et al. (115), summarizing 12 studies published between 2006-2018. Bowatte et al. (116) add to the evidence on otitis media risk in association with other pollutants than PM including 24 studies from 1975-2017 in their narrative review. Finally, Ziou et al. (117) summarized evidence from 34 studies, published between 1991 and 2021 on risk of upper respiratory tract infections URTI with short- and long-term PM exposure. However, the studies included originated from other countries than Europe.

There is strong evidence for short-term effects of ambient air pollution on various endpoints of respiratory infections in children, including ALRI, pneumonia, upper respiratory infections or otitis media (Table 35) in association with various pollutants. This is supported by the latest finding of the US EPA ISAs. Meta-analyses report significant effect estimates (Table 37). Biological plausible pathways are e.g. reduced host defense outlined in the US EPA ISAs (all). The most recent review by the HEI on long-term effects of TRAP with ALRI found moderate to high evidence for an association even though none of the studies provided information on the shape of the exposure-response function (99). A WHO report from 2018 saw *compelling* evidence for an association of air pollution with respiratory infection and consistent evidence with otitis media (19), which were also mentioned as health effects in children in the latest WHO UN compendium (21). Most reviews included a high number of studies from Europe and North America. We therefore see moderate to strong evidence for harmful effects of air pollution regarding respiratory infections in children.

**Table 35: Results of the included reviews on respiratory infections attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant(s) / focus | Main results | Evidence level by authors | Reference |
|---|---|---|---|---|---|
| ALRI | HEI (2020) | TRAP: $NO_2$, NO, NOx, BC/EC, $PM_{2.5}$, $PM_{10}$, CO | Evidence rating mainly based on consistent evidence from $NO_2$ exposure studies | moderate-high | (99) |
| Respiratory infections | US EPA (2019) | PMs | Consistent evidence for an association of overall respiratory infections with short-term $PM_{2.5}$ exposure but mixed results for categories of infections such as pneumonia. No clear evidence for long-term effects with $PM_{2.5}$. | ST: consistent, LT: some evidence but not entirely consistent | (17) |
| Respiratory infections | US EPA (2020) | Ozone | Consistent evidence of an association between short-term ozone exposure and ED visits for a variety of respiratory infection endpoints. Results for long-term effects seem protective | ST: consistent, LT: not enough studies | (23) |
| Respiratory infections | US EPA (2016) | $NO_2$, NO, Nox | Not entirely consistent results for acute effects of $NO_2$ on respiratory infections. However, biologically plausible. Some evidence for long-term effects in school children but not infants. Limited number of studies. | ST: epi not entirely consistent<br>LT: inconsiste nt in infants | (25) |
| Respiratory infections | US EPA (2017) | $SO_2$ | some, but not entirely consistent evidence supporting an association between ambient $SO_2$ concentrations and respiratory infection | ST/LT: some evidence not entirely consistent | (24) |
| Upper resp infections URTI | Ziou (2020) | LT & ST: $PM_{10}$, $PM_{2.5}$ | Robust associations with short-term $PM_{2.5}$ and $PM_{10}$ exposure | NR | (117) |
| Otitis Media | Lee (2020) | ST+LT: $PM_{10}$, PM2,5 | PM: increased risks with short-term exposure; more consistent for $PM_{2.5}$ than $PM_{10}$. Children 0–2 years of age were more vulnerable to PM exposure compared with those older than 2 years of age | NR | (115) |
| Otitis Media | Bowatte (2018) | CO, $O_3$, $NO_2$, Nox, $PM_{2.5}$, BC, $PM_{10}$, $PM_{10\text{-}2.5}$, $SO_2$ | $NO_2$ showed most consistent association. Other pollutants (PM) showed inconsistent associations | NR | (116) |

| Outcome | First author (year) | Pollutant(s) / focus | Main results | Evidence level by authors | Reference |
|---|---|---|---|---|---|
| Pneumonia | Nhung (2017) | ST: $PM_{10}$, $PM_{2.5}$, $SO_2$, $O_3$, $NO_2$, CO | $PM_{2.5}$ / $PM_{10}$: significantly increased ALRI risk with short-term exposure<br>$NO_2$: significant increases<br>Ozone: significant increases in pneumonia risk with short-term exposure to ozone<br>$SO_2$: significantly increased ALRI risk with short-term exposure | NR | (113) |
| ALRI: bronchiolitis | King (2018) | LT & ST: $PM_{10}$, $PM_{2.5}$, $NO_2$, $SO_2$, CO, $O_3$ | PM: associations with long-term exposure on the risk of hospitalization for bronchiolitis is suggested, with no evidence for short-term effects<br>$NO_2$: evidence for long-term effects stronger than for short-term effects<br>Ozone: Results for long-term effects seem protective, not results for short-term exposure<br>$SO_2$: some evidence for acute, sub-chronic, and lifetime exposure, however with low quality of studies | NR | (114) |
| ALRI | Mehta (2013) | LT: $PM_{2.5}$ | $NO_2$ showed most consistent association. Other pollutants (PM) showed inconsistent associations | NR | (111) |
| Respiratory infections | Låg (2020) | PAHs | limited number of studies suggesting a role of PAH in respiratory infections | suggestive | (112) |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 36: Characteristics of included reviews on respiratory infections attributed to ambient air pollution**

| Outcome | First author (year) | Pollutant(s) / focus | Pooled results | # studies | search date up to | DB searched | Origins of studies (#) | Publication year range | Quality tool |
|---|---|---|---|---|---|---|---|---|---|
| ALRI | HEI (2022) | TRAP: $NO_2$, NO, NOx, BC/EC, $PM_{2.5}$, $PM_{10}$, CO | yes | 27 | Jul 2019 | 2 | Europe, North America, Asia | 1995-2019 | OHAT and narrative |
| Upper resp infections URTI | Ziou (2022) | LT & ST: $PM_{10}$, $PM_{2.5}$ | yes only ST | 34 (16 in Metaanalysis) | Apr 2020-Oct 2021 | 6 | Asia, North America, Australia, SA | 1991-2021 | NOS, ST: mustafic, OHAT |
| Otitis Media | Lee (2020) | ST+LT: $PM_{10}$, PM2,5 | yes | 12 | Mar 2020 | 3 | North America, Asia, Europe | 2006-2018 | NOS |
| Otitis Media | Bowatte (2018) | CO, $O_3$, $NO_2$, Nox, $PM_{2.5}$, BC, $PM_{10}$, $PM_{10-2.5}$, $SO_2$ | no | 24 | Oct 2017 | 2 | Europe (12), North America (8), South America (1), Asia (2), other (1) | 1975-2017 | NOS |
| Pneumonia | Nhung (2017) | ST: $PM_{10}$, $PM_{2.5}$, $SO_2$, $O_3$, $NO_2$, CO | yes | 17 | Jan 2017 | 2 | Europe (2), North America (6), South America (7), Asia (1), other (1) | 1999-2016 | none |
| ALRI: bronchiolitis | King (2018) | LT & ST: $PM_{10}$, $PM_{2.5}$, $NO_2$, $SO_2$, CO, $O_3$ | no | 8 | Nov 2017 | 3 | Europe, North America, Asia | 2004-2017 | NOS, GRADE |
| ALRI | Mehta (2013) | LT: $PM_{2.5}$ | yes | 74 | Sep 2008 | 1 | 4 LT North America, Europe | 1984-2009 | none |
| Respiratory infections | Låg (2020) | PAHs | no | NR | May 2018 | 1 | North America, Europe, Asia | NR | none |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 37: Summary estimates from meta-analyses from selected reviews on respiratory infections attributed to ambient air pollution**

| Outcome | Pollutant | First author (year) | Increment of exposure [e.g. 10 µg/m³ categorial] | Metric [HR, OR, RR] | # studies or EE | Estimate | 95%-CI | Metaanalysis model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ALRI | TRAP: $NO_2$ | HEI (2022) | 10 µg/m³ | RR | 11 | **1.09** | **1.03, 1.16** | RE | 45% | 0.050 | no publication bias |
| ALRI | TRAP: EC | HEI (2022) | 1 µg/m³ | RR | 4 | 1.3 | 0.78, 2.18 | RE | 84% | <0.01 | number too low |
| URTI | ST. $PM_{2.5}$ | Ziou (2022) | 10 µg/m³ | RR | 20 | **1.01** | **1.007, 1.014** | RE | 90.40% | 0.000 | Detected, similar results after trim-and-fill |
| URTI | ST: $PM_{10}$ | Ziou (2022) | 10 µg/m³ | RR | 17 | **1.016** | **1.011, 1.216** | RE | 97.00% | 0.000 | Not clear, but similar results after trim-and-fill |
| Otitis media | $PM_{2.5}$ (ST&LT) | Lee (2020) | 10 µg/m³ | OR | 10 | **1.032** | **1.005, 1.060** | RE | 82% | <0.001 | Not detected |
| Otitis media | ST:$PM_{2.5}$ | Lee (2020) | 10 µg/m³ | OR | 6 | **1.022** | **1.007, 1.037** | RE | 69% | 0.006 | Not detected |
| Otitis media | LT:$PM_{2.5}$ | Lee (2020) | 10 µg/m³ | OR | 10 | 1.199 | 0.849, 1.693 | RE | 96% | <0.001 | Not detected |
| Otitis media | $PM_{10}$ (ST&LT) | Lee (2020) | 10 µg/m³ | OR | 6 | **1.01** | **1.008, 1.012** | RE | | | Not detected |
| Otitis media | ST:$PM_{10}$ | Lee (2020) | 10 µg/m³ | OR | 6 | **1.022** | **1.007, 1.037** | RE | 69% | 0.006 | Not detected |
| Otitis media | LT:$PM_{10}$ | Lee (2020) | 10 µg/m³ | OR | 10 | 1.199 | 0.849, 1.693 | RE | 96% | <0.001 | Not detected |
| Pneumonia | ST: $PM_{10}$* | Nhung (2017) | 10 µg/m³ | RR | 13 | **1.015** | **1.006, 1.024** | RE | 66.10% | 0.000 | not assessed |

| Outcome | Pollutant | First author (year) | Increment of exposure [e.g. 10 µg/m³ categorial] | Metric [HR, OR, RR] | # studies or EE | Estimate | 95%-CI | Metaanalysis model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pneumonia | ST: $PM_{2.5}$ | Nhung (2017) | 10 µg/m³ | RR | 13 | **1.018** | **1.005, 1.031** | RE | 38.10% | 0.080 | not assessed |
| Pneumonia | ST: $NO_2$ | Nhung (2017) | 10 ppb | RR | 12 | **1.017** | **1.004, 1.024** | RE | 71.10% | 0.000 | higher estimates in high income economies |
| Pneumonia | ST: Ozone | Nhung (2017) | 10 ppb | RR | 16 | **1.02** | **1.01, 1.03** | RE | 75.20% | 0.000 | not assessed |
| Pneumonia | ST: $SO_2$ | Nhung (2017) | 10 ppb | RR | 10 | **1.029** | **1.004, 1.053** | RE | 48.80% | 0.042 | not assessed |
| Pneumonia | ST: CO | Nhung (2017) | 1000 ppb | RR | 7 | **1.009** | **1.000, 1.019** | RE | 68.10% | 0.004 | not assessed |
| ALRI | LT: $PM_{2.5}$ | Mehta (2013) | 10 µg/m³ | RR | 4 | **1.12** | **1.03, 1.30** | Bayesian model | NR | NR | no, low number of studies |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

*Reading example for the association of emergencies due to pneumonia with $PM_{10}$ exposure (Nhungh 2017): on days with 10 ppb higher $PM_{10}$ exposure the risk for pneumonia related emergencies, e.g. hospital admission, is **significantly** increased by 1.5%, with a confidence range of the true effect between 0.6 and 2.4%. Heterogeneity $I^2$ of study results was moderate to high, indicating a some between study variation. Publication bias was not assessed in this review. Statistical significance (indicated as bold effect estimates) refers to the probability that the observed result could have occurred randomly if it has no true underlying effect. If an estimate is significant, such random occurrence is unlikely

#### Lung function & lung development

Four reviews and the integrated science assessments of the US EPA for PM (17), $NO_2$ (32), $SO_2$ (24) and Ozone (23) were included (see Table 38 to Table 40 below). The US EPA ISAs as well as a narrative review by Garcia et al. (118) were of high quality, whereas the other reviews only searched one database for their review. The review by Holm et al. (119) evaluated short- and long-term effects of ozone including studies from 2013-2021 and was therefore newer than the corresponding ISA (23). The study by Barone-Adesi et al (120) was a single study including a systematic review on lung development with $NO_2$ including studies published between 1999 to 2015. However, a risk of bias assessment was not conducted. The same is true for the review by Låg et al (112) on PAH exposure with various respiratory outcomes.

There is strong evidence for short-term effects on lung function with ozone and $NO_2$ in healthy children and those with asthma. For the latter, such decrements can lead to asthma exacerbations. There is evidence for impaired lung function development with long-term exposure to elevated $PM_{2.5}$ and TRAP showing significantly decreased lung function with long-term $NO_2$ in the pooled analysis. Regarding an exposure-response relationship, one of the reviews report a non-linear exposure-risk function with ozone exposure (119), meaning that there was an indication of threshold (of no effect) at lower exposures. Most reviews included a high number of studies from Europe and North America. The WHO publications mention lung function impairment as one of multiple effects of ambient air pollution with the 2018 report seeing “robust evidence” (19,21). Thus, the evidence for both short-term and long-term impairment of lung-function and lung function growth in children can be considered as strong.

**Table 38: Results of the included reviews on lung function attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant(s) (focus) | Main results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| ST: Lung function | US EPA (2016) | $NO_2$, NO, Nox | strong evidence for short-term effects in children with asthma, less consistent evidence in healthy children, generally consistent evidence with long-term exposure but uncertainties remain regarding independence of effects after co-pollutant adjustment ($PM_{2.5}$ | likely to be causal | (32) |
| Lung function | US EPA (2019) | PMs | limited evidence for short-term effects, but strong evidence for long-term effects of $PM_{2.5}$, suggestive evidence for $PM_{10-2.5}$ | likely to be causal | (17) |
| ST: lung function | US EPA (2020) | Ozone | causal relation of decreases of lung function with short-term exposure, | causal | (23) |
| LT: lung function | US EPA (2020) | Ozone | Inconsistent evidence from epidemiological studies for impairment of lung function growth with long-term ozone exposure, despite consistent evidence from toxicological and animal studies | inconsistent / likely | (23) |
| ST: lung function | US EPA (2017) | $SO_2$ | Weak and inconsistent evidence for an association between short-term $SO_2$ exposure and lung function impairment | inconsistent weak | (24) |
| Lung function (growth) | Garcia (2021) | ST/LT: PMs, $NO_2$, Ozone, VOC | $PM_{2.5}$: the few studies mentioned support short- and long-term effects on lung function in children<br>$NO_2$: studies showing generally effects on lung-function with short-term exposure.<br>Ozone: evidence for effects with long-term exposure not consistent | LT: most epidemiologic evidence for $PM_{2.5}$ and $NO_2$ | (118) |
| Lung Function | Holm (2022) | $O_3$ | Consistent evidence exists of small decreases in children's lung function with very low levels of short-term ozone exposure. Long-term ozone exposure decreases both lung function and lung function development in children, with non-linear exposure response function. | ST(&LT) ozone: consistent evidence | (119) |
| LT Lung function FEV1 | Barone-Adesi (2015) | LT: TRAP $NO_2$ | significant decreases with long-term $NO_2$ exposure, interpreted as TRAP | NR | (120) |
| Lung function | Låg (2020) | PAHs | Inconclusive evidence due to mixed results | inconclusive | (112) |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 39: Characteristics of included reviews on lung function attributed to ambient air pollution**

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search date up to | DB searched | Publication year range | Origin of studies (#) | Quality tool |
|---|---|---|---|---|---|---|---|---|---|
| Lung function (growth) | Garcia (2021) | ST/LT: PMs, $NO_2$, Ozone, VOC | no | 8 studies LT | 2018-Oct 2020 | 2 | LT: 2018-2020 | Europe, Asia, USA | none |
| Lung Function | Holm (2022) | $O_3$ | no | 53 | 2013-Jun 2021 | 1 | 2013-2020 | NR | yes |
| LT Lung function FEV1 | Barone-Adesi (2015) | LT: TRAP $NO_2$ | yes | 13 | 1990-2015 | 1 | 1999-2015 | Europe (8), North America (4), Asia (1) | none |
| Lung function | Låg (2020) | PAHs | no | | May 2018 | 1 | NR | North America, Europe, Asia | none |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 40: Summary estimates from meta-analyses from selected reviews on lung function attributed to ambient air pollution**

| Outcome | Pollutant | First author (year) | Increment of exposure | Metric [HR, OR, RR] | # studies or EE | Estimate | 95%-CI | Metaanalysis model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| LT Lung function FEV1 absolute | LT: TRAP $NO_2$ | Barone-Adesi (2015) | 10 µg/m3 | [ml] | 6 | **-8** | **(-14, -1)** | RE | 32% | 0.016 | No PB |
| LT Lung function FEV1 percentage decrease | LT: TRAP $NO_2$ | Barone-Adesi (2015) | 10 µg/m3 | % | 9 | **-0.7** | **(-1.1, -0.3)** | RE | NR | 0.001 | No PB |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

*Reading example for the association of lung function measured as forced expiratory volume in 1 second with $NO_2$ exposure (Barone-Adesi 2015): lung function FEV1 in children is **significantly** reduced by 8ml, with a confidence range of the true effect between 1 and 14 ml for a 10 µg/$m^3$ higher $NO_2$ long-term exposure. Heterogeneity $I^2$ of study results was low, indicating a low between study variation. Publication bias was not detected. Statistical significance (indicated as bold effect estimates) refers to the probability that the observed result could have occurred randomly if it has no true underlying effect. If an estimate is significant, such random occurrence is unlikely.

### Allergies

Five reviews and the integrated science assessments of the US EPA for PM, $NO_2$, and Ozone were included (seeTable 41 to Table 43 below). Allergic rhinitis was studied in the meta-analysis by Li et al. (121) which included publications from 2000-2020. Since this review also included adult studies, only the subgroup results for children and adolescents were extracted for all classical pollutants. Yue et al. (122) reviewed studies on eczema risk with pollution during pregnancy, including studies from 2011-2021. The review by Abolhasani et al. (123) was included to inform on eczema exacerbations due to short-term exposure to air pollution. Short-term associations of air pollution with conjunctivitis, an itchy eye disease, was studied in the review by Chen et al. (124). Three out of 12 studies included children, published between 2016 and 2017. Pooled results for the subgroup of children were available for an association with $PM_{2.5}$, $NO_2$, and ozone. Finally, a review on allergic sensitization was included from Bowatte et al. (125), showing meta-analytic results from 2 studies for $PM_{2.5}$ and $NO_2$. All studies used the Newcastle-Ottawa-Scale for study quality assessment, except for Abdolhasi et al. (123), that did not assess this. Yue et al. (122) additionally assessed risk of bias using the JBI-tool.

Overall, evidence suggests a role of air pollution on exacerbation of allergic disease with short-term exposure to air pollution, especially with $NO_2$, ozone and particulate matter supported by the US EPA's integrated science assessments (17,23–25). The study base for development of allergic disease in association with long-term exposure to air pollution is rather limited and partly supported by studies from Europe and North America. Inconsistent results regarding associations with allergies to specific allergens or co-pollutants are mentioned as arguments weakening the evidence (US EPA). Allergy development is also not mentioned in UN publications on children's health in relation to ambient air pollution (19,21,105). We consider the evidence base to be suggestive for exacerbation of allergic disease but limited for long-term effects.

**Table 41: Results of the included reviews on allergic diseases attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant(s) (focus) | Main results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| Allergic Rhinitis prevalence | Li (2022) | $PM_{2.5}$ (15 studies), $PM_{10}$ (28), $NO_2$ (27). $SO_2$ (18), Ozone (12), CO (190) | Significantly increased risk for allergic rhinitis long-term exposure to all studied pollutants. Children and adolescent are more sensitive to air pollution than adults. | NR | (121) |
| Sensitization | Bowatte (2015) | TRAP: $NO_2$, $PM_{2.5}$, BC | Some evidence for increased sensitization to aeroallergens and food with $PM_{2.5}$ and $NO_2$. Mixed results for Eczema and hayfever with all pollutants | some evidence | (125) |
| Eczema | Yue (2022) | PMs, TRAP, CO, $SO_2$, $NO_2$, ozone | Significant association between the maternal exposure to $NO_2$ and childhood eczema. No evidence for association with particulates and $SO_2$. | NR | (122) |
| Skin disorders Eczema/ atopic dermatitis (5) | Abolhasani (2021) | ST/LT:PMS, NOs2, CO, $SO_2$, $O_3$. VOC | Based on one study short-term $NO_2$ exposure increased eczema symptoms. | NR | (123) |
| ST: Conjunctivitis | Chen (2019) | $NO_2$, $PM_{2.5}$, ozone | Short-term increases of air pollution are associated with increased conjunctivits risk. The association was significant for $NO_2$ and ozone. The younger were more sensitive than adults. | yes, but not for subgroup analysis with 2-3 studies in <18y | (124) |
| allergies | US EPA (2016) | $NO_2$, NO, Nox | Inconsistent results for allergic rhinitis and hayfever with long-term exposure, but evidence for induced exacerbation of allergic airway disease in presence of allergens with short-term exposure. | | (25) |
| allergic and asthma related responses | US EPA (2020) | Ozone | Ozone enhances allergic and asthma related responses. This is supported by experimental studies in humans, and aniimal models. | likely causal | (23) |
| Allergy exacerbation | US EPA (2019) | PMs | $PM_{2.5}$-related allergy exacerbation supported by results from animal toxicological and mechanistic studies. Some evidence for an association between long-term | likely causal | (17) |

| Outcome | First author (year) | Pollutant(s) (focus) | Main results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| | | | exposure to $PM_{2.5}$ and at least some manifestations of allergic disease. | | |
| Allergy exacerbation | US EPA (2017) | $SO_2$ | Toxicological animal studies show enhanced allergic inflammation with $SO_2$ exposure but limited evidence from epidemiological studies. Some but limited evidence for a relationship between long-term $SO_2$ exposure and allergic rhinitis. | inconsistent weak | (24) |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 42: Characteristics of included reviews on allergic diseases attributed to ambient air pollution**

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search up to | DB searched | Publication year range | Origin of studies (#) | Quality tool |
|---|---|---|---|---|---|---|---|---|---|
| Allergic Rhinitis prevalence | Li (2022) | $PM_{2.5}$ (15 studies), $PM_{10}$ (28), $NO_2$ (27). $SO_2$ (18), Ozone (12), CO (190) | yes | 35 | Dec 2020 | 3 | 2000-2020 | Asia (19), Europe (15) North America 1 | NOS, JBI |
| Sensitization | Bowatte (2015) | TRAP: $NO_2$, $PM_{2.5}$, BC | yes | 5 | Mar 2014 | 3 | 2007-2013 | Europe (7), North America (4) | NOS |
| Eczema | Yue (2022) | PMs, TRAP, CO, $SO_2$, $NO_2$, ozone | yes | 12 | Oct 2021 | 4 | 2011-2021 | Asia (8), Europe (4), North America | NOS |
| Skin disorders Eczema/ atopic dermatitis (5) | Abolhasani (2021) | ST/LT:PMs, NOs2, CO, $SO_2$, $O_3$, VOC | no | 5 in children | 1985-2020 | 4 | NR | Asia | none |
| ST: Conjunctivitis | Chen (2019) | $NO_2$, $PM_{2.5}$, ozone | yes | 12 (3 children) | Mar 2019 | 4 | children: 2016-2017 | children studies: 2 Asia, 1 North America | NOS |
| Allergies | US EPA (2016) | $NO_2$, NO, Nox | no | | Aug 2014 | HERO database | NR | NR | yes |
| Allergic and asthma related responses | US EPA (2020) | Ozone | no | | Mar 2018 | HERO database | NR | NR | yes |
| Allergy exacerbation | US EPA (2019) | PMs | no | | Feb 2015 | HERO database | | | yes |
| Allergy exacerbation | US EPA (2017) | $SO_2$ | no | | Aug 2016 | HERO database | | | yes |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 43: Summary estimates from meta-analyses from selected reviews on allergic diseases attributed to ambient air pollution**

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric [HR, OR, RR] | Estimate | 95%-CI | Model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Allergic Rhinitis prevalence | $PM_{2.5}$ | Li (2022) | 10 µg/m3 | 11 | OR | **1.11** | **1.06, 1.16** | RE | 6.57% | 0.035 | NR |
| Allergic Rhinitis prevalence | $PM_{10}$ | Li (2022) | 10 µg/m3 | 22 | OR | **1.12** | **1.06, 1.19** | RE | 93.70% | 0.000 | NR |
| Allergic Rhinitis prevalence | $NO_2$ | Li (2022) | 10 µg/m3 | 24 | OR | **1.14** | **1.07, 1.22** | RE | 82.12% | 0.000 | NR |
| Allergic Rhinitis prevalence | $SO_2$* | Li (2022) | 10 µg/m3 | 16 | OR | **1.13** | **1.03, 1.24** | RE | 83.30% | <0.001 | NR |
| Allergic Rhinitis prevalence | Ozone | Li (2022) | 10 µg/m3 | 9 | OR | **1.05** | **1.01, 1.09** | RE | 87.30% | <0.001 | NR |
| Allergic Rhinitis prevalence | CO | Li (2022) | 100 µg/m3 | 8 | OR | 1.08 | 0.97, 1.20 | RE | 97.20% | <0.001 | NR |
| Sensitization food allergen (age of 8) | TRAP: $NO_2$, $PM_{2.5}$, BC | Bowatte (2015) | 10 µg/m3 | 2 | OR | **1.19** | **1.00, 1.42** | RE | 0.00% | 0.779 | Not assessed |
| Sensitization food allergen (age of 8) | TRAP: $NO_2$, $PM_{2.5}$, BC | Bowatte (2015) | 10 µg/m3 | 2 | OR | **1.18** | **1.00, 1.39** | FE | 0.00% | 0.474 | Not assessed |
| Eczema | $PM_{10}$ entire pregnancy | Yue (2022) | 10 µg/m3 | 8 | OR/RR | 0.98 | 0.90, 1.07 | RE | 54.50% | 0.032 | no pub bias |
| Eczema | $PM_{2.5}$ entire pregnancy | Yue (2022) | 10 µg/m3 | 4 | OR/RR | 1.14 | 0.89, 1.45 | RE | 46.00% | 0.916 | NR, low number? |
| Eczema | $NO_2$ entire pregnancy | Yue (2022) | 10 µg/m3 | 9 | OR/RR | **1.13** | **1.06, 1.19** | RE | 41.30% | 0.092 | asymmetry but not sig |
| Eczema | $SO_2$ entire pregnancy | Yue (2022) | 10 µg/m3 | 4 | OR/RR | 1.03 | 0.98, 1.07 | RE | 0.00% | 0.773 | NR, low number? |

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric [HR, OR, RR] | Estimate | 95%-CI | Model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ST: Conjunctivitis | $PM_{2.5}$ | Chen (2019) | 10 µg/m3 | 2 | RR | 1.0086 | 0.9845, 1.0332 | RE | 64.30% | 0.094 | not assessed in subgroup |
| ST: Conjunctivitis | $NO_2$ | Chen (2019) | 10 µg/m3 | 3 | RR | **1.0472** | **1.0249, 1.0700** | RE | 42.40% | 0.203 | not assessed in subgroup |
| ST: Conjunctivitis | Ozone | Chen (2019) | 10 µg/m3 | 3 | RR | **1.0357** | **1.0156, 1.0561** | RE | 72.10% | 0.016 | not assessed in subgroup |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

*Reading example for the association of allergic rhinitis risk with $SO_2$ exposure (Li 2022): the risk of allergic rhinitis is **significantly** increased by 13%, with a confidence range of the true effect between 3 and 14% for a 10 µg/m3 higher $SO_2$ exposure. Heterogeneity $I^2$ of study results was high, indicating a high between study variation. Publication bias was not assessed in this review. Statistical significance (indicated as bold effect estimates) refers to the probability that the observed result could have occurred randomly if it has no true underlying effect. If an estimate is significant, such random occurrence is unlikely.

#### Asthma and asthma development

Asthma in children is a widely studied outcome in relation to air pollution and a number of high quality reviews were selected (see Table 44 to Table 46 below). The latest evidence stems from the comprehensive review by the HEI studying long-term effects of TRAP with asthma related outcomes. Meta-analysis, risk of bias assessment and an evidence synthesis following OHAT and a narrative approach considering all available studies were conducted. Asthma development was studied in 25 studies, published between 2007 and 2019. Prevalence of asthma ever([1]) covering 45 studies published between 1993 and 2019 and active asthma([2]) with medication or symptoms during the last 12 months and wheeze were studied in 34 studies published between 1999 and 2019. Han et al. (126) added meta-analytic evidence on Benzene and VOC with 4 and 2 studies, respectively. Study quality was assessed using the navigation guide. Association with ambient $PM_{2.5}$ and the timing of exposure were studied in Bettiol et al. (127) and Yan et al (128) including 26 and 18 studies published between 2002 and 2019. Both reviews used the Newcastle-Ottawa Scale for quality assessment. The review by Buteau et al (129) looked into industrial air pollution as a contributor to asthma development or asthma ever, including studies from 2000 to 2017. A systematic analysis of study quality was not conducted. Zu et al. (130) studied asthma development in relation to long-term ozone exposure narratively summarizing 11 studies in children and adolescents. Finally, Låg et al (112) studied associations with PAH exposure with various respiratory endpoints including asthma. In this review only one database was searched and no formal risk of bias assessment was conducted.

Overall, there is compelling evidence for an association of long-term exposure to air pollution and asthma, especially for PM and $NO_2$, which the US EPA consider to be likely causal relationships. Additionally, the HEI traffic review considered the evidence for an association of TRAP with asthma onset to be moderate to high relying on significant associations in meta-analyses, positive associations with indirect traffic measures and monotonic exposure-response functions found in two studies. Of note, is the high number of European and North America n studies backing this relationship. Additionally, this epidemiological evidence is backed with plausible biological pathways found in experimental, animal and toxicological studies. This is in line with statements in various UN publications on children's health (19,21,105). Most reviews included a high number of studies from Europe and North America. They showed strong evidence for the development of asthma or asthma-like symptoms in relation to long-term air pollution.

([1]) Asthma ever is a category of disease that has been assessed in cross-sectional studies asking has your child ever been diagnosed with asthma. It does not necessarily mean that the child still suffers from the condition.

([2]) Active asthma is a condition defined as a child being diagnosed with asthma and still taking medication or showing symptoms in the last 12 months of assessment.

**Table 44: Results of the included reviews on asthma and asthma related diseases attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant(s) (focus) | Selected results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| Prevalence of Asthma ever | HEI (2022) | TRAP: $NO_2$, NO, NOx, BC/EC, $PM_{2.5}$, $PM_{10}$, CO | Evidence for an association of asthma prevalence or development with TRAP was moderate to high, mainly based on effects with $NO_2$ exposure. Evidence was very low to low for other traffic related pollutants such as $PM_{2.5}$ or EC. | moderate | (99) |
| LT Respiratory | US EPA (2010) | CO | Inadequate evidence for long-term effects | ST: suggestive, LT: inadequate | (32) |
| Asthma development | US EPA (2016) | $NO_2$, NO, Nox | Strong evidence for an association with asthma with uncertainties regarding independence of effects from other pollutants. | likely to be causal | (25) |
| Asthma development LT | US EPA (2019) | PMs | The evidence from epidemiologic studies on asthma related outcomes is more limited than for other respiratory outcomes. It indicated associations between long-term $PM_{2.5}$ exposure and asthma development in children, asthma prevalence in children, and childhood wheeze. | likely (more limited evidence) | (17) |
| LT: asthma development | US EPA (2020) | Ozone | Epidemiological studies show generally consistent evidence for associations of long-term ozone exposure with the development of asthma in children. | likely to be causal | (23) |
| LT: asthma development | US EPA (2017) | $SO_2$ | Coherent evidence for an association of asthma development with long-term exposure | suggestive | (24) |
| Asthma development | Han (2021) | TRAP: $PM_{2.5}$, $NO_2$, VOC, Benzene | Significantly increased risks of asthma development with traffic-related $PM_{2.5}$ and $NO_2$ exposure as well as benzene and VOC exposure | NR | (126) |
| Asthma and Wheeze Development | Bettiol (2021) | TRAP: PMs, UFP, NOs, BC, CO | Consistent evidence for an association of prenatal PM exposure and development of asthma in children, less consistent evidence for post-natal exposure | NR | (127) |
| Asthma and Wheeze Development | Yan (2020) | $PM_{2.5}$ | $PM_{2.5}$: Non-significantly increased risk of asthma development mit pre-natal exposure. | NR | (128) |

| Outcome | First author (year) | Pollutant(s) (focus) | Selected results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| Asthma development | Zu (2018) | Ozone | Inconsistent findings in epidemiological studies additionally lacking in study quality. | NR | (130) |
| Asthma development | Låg (2020) | PAHs | Study results support an association with asthma development in children. Associations were not limited to B[a]P, but also encompassed low-molecular weight PAHs such as naphthalene, phenanthrene, and pyrene. | NR | (112) |

## Table 45: Characteristics of included reviews on asthma attributed to ambient air pollution

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search up to | DB searched | Publication year range | Origin of studies (#) | Quality tool |
|---|---|---|---|---|---|---|---|---|---|
| Prevalence of Asthma ever | HEI (2022) | TRAP: $NO_2$, NO, NOx, BC/EC, $PM_{2.5}$, $PM_{10}$, CO | yes | 45 | Jul 2019 | 2 | 1993-2019 | Europe, North America, Asia | OHAT and narrative |
| Prevalence of Active Asthma | HEI (2022) | TRAP: $NO_2$, NO, NOx, BC/EC, $PM_{2.5}$, $PM_{10}$, CO, Benzene | yes | 34 | Jul 2019 | 2 | 1999-2019 | Europe (9), North America, Asia | OHAT and narrative |
| Asthma onset (incidence) | HEI (2022) | TRAP: $NO_2$, NO, NOx, BC/EC, $PM_{2.5}$, $PM_{10}$, CO | yes | 25 | Jul 2019 | 2 | 2007-2019 | Europe, North America, Asia | OHAT and narrative |
| Asthma development | Han (2021) | TRAP: $PM_{2.5}$, $NO_2$, VOC, Benzene | yes | 27 | Jan 2000-Jan 2019 | 3 | 2000-2019 | Europe (16), North America (2), Asia (9) | Navigation Guide |
| Asthma and Wheeze Development | Bettiol (2021) | TRAP: PMs, UFP, NOs, BC, CO | no | 26 | Jan 2000-May 2020 | 2 | 2002-2020 | Europe (10), North America (8), Asia (2), Mexico (1) | NOS |
| Asthma and Wheeze Development | Yan (2020) | $PM_{2.5}$ | yes | 9 | Jul 2019 | 4 | 2010-2019 | Europe 10), North America (12), South America (5), Asia (3), Africa (2) | NOS |
| Asthma development | Zu (2018) | Ozone | no | 14 (11 children) | Oct 2017 | 2 | 2008-2016 | NA (7), Asia (3) 1 pooled North America/EU | OHAT, IRIS, STROBE |
| Asthma development | Låg (2020) | PAHs | no | NR | May 2018 | 1 | NR | North America, Europe, Asia | none |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 46: Summary estimates from meta-analyses from selected reviews on various asthma endpoints attributed to ambient air pollution**

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric [HR, OR, RR] | Estimate | 95%-CI | Model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Asthma ever | TRAP: $NO_2$ | HEI (2022) | 10 µg/m3 | 21 | RR | **1.09** | **1.01, 1.18** | RE | 55% | 0.009 | no publication bias |
| Asthma ever | TRAP: NOx | HEI (2022) | 20 µg/m3 | 6 | RR | 1.02 | 0.99, 1.05 | RE | 0% | 0.830 | number too low |
| Asthma ever | TRAP: EC | HEI (2022) | 1 µg/m3 | 3 | RR | 1.3 | 0.56, 3.04 | RE | 30% | 0.240 | number too low |
| Asthma ever | TRAP: $PM_{10}$ | HEI (2022) | 10 µg/m3 | 5 | RR | 0.95 | 0.64, 140 | RE | 68% | 0.010 | number too low |
| Asthma ever | TRAP: $PM_{2.5}$ | HEI (2022) | 5 µg/m3 | 3 | RR | 1.29 | 0.58, 2.87 | RE | 0% | 0.410 | number too low |
| Asthma ever | TRAP: CO | HEI (2022) | 1 mg/m3 | 3 | RR | **1.5** | **1.03, 2.17** | RE | 0% | 0.540 | number too low |
| Active asthma | TRAP: $NO_2$* | HEI (2022) | 10 µg/m3 | 12 | RR | **1.12** | **1.02, 1.23** | RE | 49% | 0.030 | no publication bias |
| Active asthma | TRAP: NOx | HEI (2022) | 20 µg/m3 | 3 | RR | 1.03 | 0.97, 1.09 | RE | 0% | 0.770 | number too low |
| Active asthma | TRAP EC | HEI (2022) | 1 µg/m3 | 3 | RR | 1.25 | 0.98, 1.59 | RE | 0% | 0.720 | number too low |
| Active asthma | TRAP $PM_{10}$ | HEI (2022) | 10 µg/m3 | 4 | RR | 0.96 | 0.70, 1.31 | RE | 36% | 0.200 | number too low |
| Asthma onset | TRAP: $NO_2$ | HEI (2022) | 10 µg/m3 | 12 | RR | 1.05 | 0.99, 1.12 | RE | 73% | <0.01 | no publication bias |
| Asthma onset | TRAP: Nox | HEI (2022) | 20 µg/m3 | 3 | RR | 1.25 | 0.52, 3.01 | RE | 90% | 0.109 | number too low |
| Asthma onset | TRAP: EC | HEI (2022) | 1 µg/m3 | 5 | RR | 1.11 | 0.94, 1.31 | RE | 47% | 0.110 | number too low |
| Asthma onset | TRAP: $PM_{2.5}$ | HEI (2022) | 5 µg/m3 | 5 | RR | 1.33 | 0.90, 1.98 | RE | 67% | 0.020 | number too low |
| Asthma development | TRAP $PM_{2.5}$ | Han (2021) | NR | 15 | OR | **1.07** | **1.00, 1.13** | RE | 29% | 0.040 | no publication bias |
| Asthma development | TRAP $PM_{2.5}$ cohort studies | Han (2021) | NR | 11 | OR | **1.11** | **1.01, 1.22** | RE | 49% | 0.030 | no publication bias |
| Asthma development | TRAP $NO_2$ | Han (2021) | NR | 22 | OR | **1.11** | **1.06, 1.17** | RE | 50% | 0.003 | no publication bias |
| Asthma development | TRAP $NO_2$ cohort studies | Han (2021) | NR | 15 | OR | **1.1** | **1.03, 1.16** | RE | 50% | 0.003 | no publication bias |

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric [HR, OR, RR] | Estimate | 95%-CI | Model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Asthma development | Benzene | Han (2021) | NR | 4 | OR | **1.21** | **1.12, 1.31** | FE | 0% | <0.0001 | no publication bias |
| Asthma development | VOC | Han (2021) | NR | 2 | OR | **1.06** | **1.03, 1.10** | FE | 0% | 0.001 | no publication bias |
| asthma and wheezing | $PM_{2.5}$ prenatal | Yan (2020) | 5 µg/m3 | 10 | OR | **1.06** | **1.02, 1.11** | RE | 83.10 % | 0.000 | no publication bias |
| asthma | $PM_{2.5}$ entire pregnancy | Yan (2020) | 5 µg/m3 | 4 | OR | 1.06 | 0.98, 1.14 | RE | 84.60 % | <0.001 | no publication bias |
| wheezing | $PM_{2.5}$ prenatal | Yan (2020) | 5 µg/m3 | 5 | OR | **1.08** | **1.01, 1.15** | RE | 82.60 % | <0.001 | no publication bias |
| asthma hospitalisation | ST: $PM_{2.5}$ industry | Buteau (2019) | 10 µg/m3 | 4 | OR | 1.02 | 0.93, 1.10 | RE | 56.20 % | 0.077 | NR |
| bronchiolitis hospitalisation | ST: $PM_{2.5}$ industry | Buteau (2019) | 10 µg/m3 | 4 | OR | 1.01 | 0.98, 1.03 | RE | 32.50 % | 0.217 | NR |
| asthma hospitalisation | ST: $SO_2$ industry | Buteau (2019) | 10 ppb | 5 | OR | 1.02 | 0.96, 1.08 | RE | 55.70 % | 0.060 | NR |
| bronchiolitis hospitalisation | ST: $SO_2$ industry | Buteau (2019) | 10 ppb | 5 | OR | 1.01 | 0.97, 1.05 | RE | 63.80 % | 0.026 | NR |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

*Reading example for the association of active asthma, current medicated asthma or asthma with symptoms, with traffic-related air pollution ($NO_2$) exposure (HEI 2022): the risk of active asthma is **significantly** increased by 12%, with a confidence range of the true effect between 2 and 23% for a 10 µg/m3 higher $NO_2$ exposure. Heterogeneity $I^2$ of study results was moderate, indicating some between study variation. Publication bias was not detected. Statistical significance (indicated as bold effect estimates) refers to the probability that the observed result could have occurred randomly if it has no true underlying effect. If an estimate is significant, such random occurrence is unlikely

#### Asthma exacerbation and respiratory emergencies

Short-term effects regarding emergency department visits or hospitalizations due to asthma were reviewed in 4 publications including meta-analysis and the US EPA's integrated science assessments (17,23,24,24,25) as well as the HEI TRAP review (99) (see Table 47 to Table 49 below). The WHO review by Zheng et al. (131) presented subgroup results for children, including 24 studies on NO2, 32 studies on ozone and 26 studies studying SO2 and children's emergency department visits up to the end of the search in August 2018. Study quality was assessed following the adapted GRADE methodology. The review by Huang et al. (132), including studies up to August 2020, presented additional subgroup results on PM10 and CO. Study quality assessment was conducted based on a method based on the Newcastle-Ottawa Scale and the Cochrane risk of bias tool handbook developed by Mustafic et al (133). A review by Lim et al. (134) presented the most comprehensive data on asthma emergencies due to PM2.5 searched up to 2016, including 26 children studies. Quality assessment was not reported in this review. However, subgroup analysis to study sources of heterogeneity and publication bias were conducted.

There is strong evidence for increased hospital admissions and emergency department visits due to asthma with short-term exposure to ambient air pollution based on a considerable number of studies from Europe and North America. The evidence is specifically strong for an association with particulate matter, $NO_2$, and ozone and considered to be causally related to these pollutants. This is supported by multiple epidemiological studies, plausible underlying biological mechanisms and studies reporting mostly linear exposure-response functions. This corresponds to statement in various UN publications on children's health (19,21,105).

**Table 47: Results of the included reviews on asthma related emergencies attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant(s) (focus) | Selected results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| LT Asthma exacerbation in children | HEI (2022) | TRAP: $NO_2$, NOx, BC/EC, $PM_{2.5}$, CO | limited evidence of an associations between traffic pollutants and asthma exacerbation in children | LT:TRAP low | (99) |
| ST: asthma exacerbation | US EPA (2019) | PMs | strong evidence for an association of short-term $PM_{2.5}$ exposure with exacerbation of asthma, with some uncertainties regarding independent effects from co-pollutants. | causal | (17) |
| ST: Asthma Exacerbation | US EPA (2016) | $NO_2$, NO, NOx | Multiple lines of evidence support a relationship between short-term $NO_2$ exposure and asthma exacerbation | causal | (25) |
| ST Respiratory | US EPA (2010) | CO | Some evidence for an association with short-term CO-exposure from children studies | ST: suggestive, LT: inadequate | (32) |
| ST. Asthma exacerbation | US EPA (2019) | $SO_2$ | Positive associations for asthma hospital admissions and emergency department visits with short-term $SO_2$ exposures, specifically for children. | causal | (24) |
| ST:asthma emergencies | US EPA (2020) | Ozone | Strong evidence from both epidemiological studies and panel or experimental studies and respiratory hospital admissions and ED visits, especially in children. | causal | (23) |
| ST: Asthma hospitalization and infections, LT: Asthma ever, Wheeze, Asthma development | Buteau (2019) | Industrial pollution: $PM_{2.5}$, proximity, $SO_2$, $NO_2PM_{10}$, $PM_{10-2.5}$ - few studies, low evidence ns increased risk | Some evidence for increase asthma exacerbation with proximity to industries. | ST: no evidence, indication of LT effects | (129) |
| ST Asthma Emergencies | Zheng (2021) | ST: $O_3$, $NO_2$, $SO_2$ | Significantly increased risks of asthma exacerbation with $NO_2$, $SO_2$ and ozone with weaker evidence for an association with $SO_2$ in an all age analyses. Children and adolescents seemed more susceptible. | $O_3$ and $NO_2$: high, $SO_2$ moderate | (131) |
| ST Asthma Emergencies | Huang (2021) | PMs, $SO_2$, $NO_2$, CO, $O_3$ | Significantly increased risks with short-term exposure to particulates, $SO_2$, CO and elevated risks with $NO_2$ and ozone exposure. Generally stronger effects in children than adults. | yes | (132) |

| Outcome | First author (year) | Pollutant(s) (focus) | Selected results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| ST Asthma Emergencies | Li (2019) | UFPs | Significantly increased risk with short-term exposures to UFP | may increase (significant) | (135) |
| ST Asthma Emergencies | Lim (2016) | $PM_{2.5}$ | Significantly increased risk with short-term exposures to $PM_{2.5}$ | NR | (134) |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 48: Characteristics of included reviews on asthma related emergencies attributed to ambient air pollution**

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search date up to | DB searched | Publication year range | Origin of studies | a risk of bias assessment tool used |
|---|---|---|---|---|---|---|---|---|---|
| LT Asthma exacerbation in children | HEI (2022) | TRAP: $NO_2$, NOx, BC/EC, $PM_{2.5}$, CO | no | 6 | Jul 2019 | 2 | 2009-2019 | North America (5), Asia (1) | OHAT and narrative |
| ST: Asthma hospitalization and infections, LT: Asthma ever, Wheeze, Asthma development | Buteau (2019) | Industrial pollution: $PM_{2.5}$, proximity, $SO_2$, $NO_2PM_{10}$, $PM_{10-2.5}$ - few studies, low evidence ns increased risk | yes | 67 (48 on children) | Jan 2000-Sep 2017 | 4 | 2000-2017 | Europe 10), North America (12), South America (5), Asia (3), Africa (2) | not systematically assessed, discussed (considering rather low quality of studies) |
| ST Asthma Emergencies | Zheng (2021) | ST: $O_3$, $NO_2$, $SO_2$ | yes | 31 | Aug 2018 | 7 | NR | Most studies from Europe and North America | GRADE WHO |
| ST Asthma Emergencies | Huang (2021) | PMs, $SO_2$, $NO_2$, CO, $O_3$ | yes | 84 (10 $PM_{2.5}$ children) | Aug 2020 | 8 | NR | NR | Mustafic score (2012) |
| ST Asthma Emergencies | Li (2019) | UFPs | yes | 8 | Mar 2018 | 4 | | Europe (6), North America (1), Australia (2) | Agency of Health Care Research Assessment Scale, NOS, Mustafic |
| ST Asthma Emergencies | Lim (2016) | $PM_{2.5}$ | yes | 26 | Mar 2016 | 2 | 1999-2016 | Europe (8), North America (14), Asia (3) | none |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 49: Summary estimates from meta-analyses from selected reviews on asthma related emergencies attributed to ambient air pollution**

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric [HR, OR, RR] | Estimate | 95%-CI | Model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ERV or HA due to asthma | ST: $NO_2$ | Zheng (2021) | 10 µg/m3 | 24 | RR | **1.02** | **1.011, 1.029** | RE | NR | NR | no clear evidence for publication bias |
| ERV or HA due to asthma | ST: $O_3$* | Zheng (2021) | 10 µg/m3 | 32 | RR | **1.009** | **1.002, 1.017** | RE | NR | NR | no clear evidence for publication bias |
| ERV or HA due to asthma | ST: $SO_2$ | Zheng (2021) | 10 µg/m3 | 26 | RR | **1.021** | **1.011, 1.032** | RE | NR | NR | no clear evidence for publication bias |
| asthma exacerbation | $PM_{10}$ | Huang (2021) | 10 µg/m3 | 11 | RR | **1.027** | **1.002, 1.052** | RE | 83.10% | 0.000 | not reported in subgroup results in children |
| asthma exacerbation | CO | Huang (2021) | 1 mg/m3 | 6 | RR | **1.022** | **1.002, 1.041** | RE | 67.10% | 0.010 | not reported in subgroup results in children |
| asthma exacerbation | UFPs | Li (2019) | 10000 particles/cm3 | 9 | OR | **1.07** | **1.037, 1.104** | FE | 0.00% | 0.451 | Publication bias not detected, trim-and-fill of 3 studies did not change results |
| ERV or HA due to asthma | $PM_{2.5}$ | Lim (2016) | 10 µg/m3 | 26 | RR | **1.05** | **1.03, 1.07** | RE | 95.70% | <0.0001 | no publication bias |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

*Reading example for the association of emergencies due to asthma with short-term ozone exposure (Nhungh 2017): on days with a 10 µg/m3 higher ozone exposure the risk for emergency visits or hospital admission due to asthma, is **significantly** increased by 0.9%, with a confidence range of the true effect between 0.2 and 1.7%. Heterogeneity $I^2$ of study results was not reported. Publication bias was not assessed in this review. Statistical significance (indicated as bold effect estimates) refers to the probability that the observed result could have occurred randomly if it has no true underlying effect. If an estimate is significant, such random occurrence is unlikely

### *Neurologic effects*

#### Neurodevelopment and cognitive function

Four reviews were included with additional information from the US EPA ISA on particulates and the HEI TRAP review (see Table 50 to Table 52 below). The association between academic performance and road traffic density, $NO_2$, ozone and $PM_{2.5}$ was investigated by Stenson et al. (136). They found 10 studies published between 2015 and 2020 and assessed the evidence according to OHAT. Shang et al. (137) was included for $NO_2$ and cognitive and psychomotor development, analyzed in 10 studies published 2012-2019. Quality assessment was conducted following standards set by the Cochrane collaboration. Two reviews were included for a variety of outcomes regarding neurodevelopmental skills and executive function associated with TRAP covering 13 studies published between 2012-2018 (138) and 30 studies published between 2008-2019 (139). Gartland et al. (138) examined the quality of studies with the Newcastle-Ottawa scale and narratively assessed the evidence for all included traffic-related air pollutants ($PM_{2.5}$, $PM_{10}$, EC, BC, $NO_2$, NOx, ozone, CO, PAHs and UFP). Castagna et al. (139) evaluated the risk of bias according to OHAT, but did not assess the evidence. Only Shang et al. (137) presented pooled results. Additionally, we included the HEI report (99), which narratively discusses the evidence based on 30 studies on TRAP. Furthermore, the USA EPAs Integrated Science Assessment for PM (17) was also taken into account.

Overall, findings indicate that air pollution, especially $PM_{2.5}$, $NO_2$, EC and PAH are associated with poorer cognitive development in children based on studies from mainly Europe or North America. The confidence in the body of evidence for academic performance was low according to Stenson et al. (136). The US EPA saw mixed effects in a limited number of children studies. Based on toxicological animal studies and more consistent effect on cognitive impairment in adults the evidence for a causal relationship with particulates was deemed likely to be causal. The most recent evidence from the HEI report (99) based on 30 studies with more than half of them being cohort studies was rated *moderate*. The most suggestive relationships were found for attention, executive function and memory. There is emerging evidence on impaired neurodevelopment in children associated with air pollution. We consider the evidence to be moderate with emerging evidence.

**Table 50: Results of the included reviews on neurodevelopment and cognitive function attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant(s) (focus) | Selected results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| Cognitive function domains, IQ, behavior | Shang (2020) | prenatal $NO_2$ | Prenatal $NO_2$ was significantly associated with impaired psychomotor function but not significantly with global cognition or language. | NR | (137) |
| Cognitive measures: attention, scores, memory | Gartland (2022) | TRAP: PMs, UFP, Nos, Ozone, PAH, CO | Indication of effects on executive function and academic achievement ($PM_{2.5}$), on working memory ($NO_2$), less evidence on $PM_{10}$ suggesting effects on attention, reasoning, and academic test scores | limited | (138) |
| Cognitive function, neuro-development, skills | Castagna (2022) | $NO_2$, PMs. BC, PAH | Detrimental effects of air pollutants on children's neurodevelopmental skills, not clinically relevant, especially global intellective functioning and attention/executive function. Pre- ans postnatal exposure seem relevant | NR | (139) |
| Cognitive: Academic performance | Stenson (2021) | TRAP: Road densitiy, $NO_2$, Ozone, $PM_{2.5}$ | Poorer student academic performance in association with TRAP. No consistent patterns für specific pollutant, high risk of bias. | low | (136) |
| Cognitive Function | HEI (2022) | TRAP: $NO_2$, Nox, EC, $PM_{2.5}$, $PM_{10}$PAH/Benzene, proximity | Exposure to individual TRAP pollutants (namely, $NO_2$, EC, and $PM_{2.5}$) a bit less than half the studies found evidence for associations with poorer cognitive function, including general intelligence, attention, and working memory; for both pregnancy and childhood exposure. Some but limited evidence for associations with source-specific components of PM, $PM_{10}$, PMcoarse, and UFPs. | moderate | (99) |
| Cognitive development | US EPA (2019) | PMs | Limited and inconsistent epidemiologic evidence for neurodevelopmental outcomes in children, biologically plausble effects, effects in adults for cognitive impairment stronger | likely causal | (17) |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 51: Characteristics of included reviews on neurodevelopment and cognitive function attributed to ambient air pollution**

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search up to | DB searched | Publication year range | Origin of studies (#) | Quality tool |
|---|---|---|---|---|---|---|---|---|---|
| Cognitive function domains, IQ, behavior | Shang (2020) | prenatal $NO_2$ | Yes | 10 | May 2019 | 4 | 2012-2019 | Europe, Asia | Lam et al. / Cochrane |
| Cognitive measures: attention, scores, memory | Gartland (2022) | TRAP: PMs, UFP, Nos, Ozone, PAH, CO | no | 13 | Feb 2020 | 3 | 2012-2018 | Europe, North America, SA | PROSPERO |
| Cognitive function, neurodevelopment, skills | Castagna (2022) | $NO_2$, PMs. BC, PAH | no | 30 | Sep 2021 | 4 | 2008-2019 | Europe (23), North America (9), Mexico, Teheran | PROSPERO |
| Cognitive: Academic performance | Stenson (2021) | TRAP: Road densitiy, $NO_2$, Ozone, $PM_{2.5}$ | no | 10 | Jun 2020 | 8 | 2015-2020 | North America (9), Europe | PROSPERO |
| Cognitive Function | HEI (2022) | TRAP: $NO_2$, Nox, EC, $PM_{2.5}$, $PM_{10}$, PAH/Benzene, proximity | no | 30 | Jul 2019 | 2 | 2008-2019 | - | OHAT |
| Cognitive development | US EPA (2019) | PMs | no | | Feb 2015 | HERO database | - | - | - |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 52: Summary estimates from meta-analyses from selected reviews on neurodevelopment and cognitive function attributed to ambient air pollution**

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric [HR, OR, RR] | Estimate | 95%-CI | Model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| general cognition | prenatal $NO_2$ | Shang (2020) | 10 µg/m3 | 8 | point decrease | -0.33 | -1.02, 0.37 | RE | 28.76% | NR | low report bias |
| language | prenatal $NO_2$ | Shang (2020) | 10 µg/m3 | 9 | point decrease | -0.13 | -0.34, 0.60 | RE | 14.16% | NR | low report bias |
| global psychomotor | Prenatal $NO_2$* | Shang (2020) | 10 µg/m3 | 12 | point decrease | **-0.76** | **-1.34, -0.18** | RE | 36.98 | NR | low report bias |
| fine psychomotor | prenatal $NO_2$ | Shang (2020) | 10 µg/m3 | 8 | point decrease | **-0.62** | **-1.09, -0.16** | RE | 0 | NR | low report bias |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

*Reading example for the association of global psychomotor abilities with $NO_2$ exposure (Shang 2020): the global psychomotor abilities is **significantly** reduced by 0.76 pints, with a confidence range of the true effect between 0.18 and 1.34 for a 10 µg/m3 higher $NO_2$ exposure. Heterogeneity $I^2$ of study results was low, indicating a low between study variation. Publication bias was not detected. Statistical significance (indicated as bold effect estimates) refers to the probability that the observed result could have occurred randomly if it has no true underlying effect. If an estimate is significant, such random occurrence is unlikely

### Autism spectrum disorder

Autism is a condition that includes a spectrum of impairments affecting social interaction, language development, and communication skills and that often involves rigid and repetitive behaviors (US EPA ISA PM 2019). Three reviews (99,140,141) and the integrated science assessments of the US EPA for PM, $NO_2$ and ozone (17,23,25) were included (see Table 53 to Table 55 below). Lin et al (140) provided pooled results for $PM_{2.5}$ and $PM_{10}$ at various time points from pregnancy up to 2 years of age with autism spectrum disorder (ASD). It included 31 studies published 2013-2022, including studies on ADHD. The review by Dutheil et al. (141) included less studies, published between 2013 and 2020, and therefore only was used for the NOx results. The HEI review (2022) provided a narrative review on the evidence of TRAP with ASD including 14 studies from 2013-2019. The US EPA ISAs, the HEI TRAP review as well as the review by Lin et al. (140) were of high quality, assessing risk of bias and the level of evidence with standardized methods such as GRADE. The review by Dutheil et al. (141) used an interesting method for meta-analysis of results combining either all reported effect estimates of an exposure-outcome, or the lowest (pessimistic model) or the highest effect estimates (optimistic model) in separate models, respectively.

Overall, there is emerging evidence on associations of autism spectrum disorder with strongest results for $PM_{2.5}$ and $NO_2$. Studies were mainly conducted in North America or Europe. Uncertainties remain regarding co-pollutant exposures like noise or other air pollutants, exposure time windows, with evidence pointing towards effects with post-natal exposure (140). The most recent review by HEI rates the evidence level moderate-high for associations with TRAP. Oxidative stress and neuroinflammation are among proposed mechanisms, but this remains to be elucidated in future studies. Effects on the brain and development of children are mentioned by all UN-reports (21). The WHO report remarks on a growing body of research that suggests such associations (19). If such associations are causally related to air pollution the effects are of fundamental significance. Therefore, the evidence can be considered as moderate with emerging evidence.

**Table 53: Results of the included reviews on autism spectrum disorder attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant(s) (focus) | Selected results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| ASD | Dutheil (2021) | $PM_{10}$, $PM_{2.5}$, Nox, metals, Ozone | Significantly increased risks in "optimistic" models with $PM_{2.5}$, $PM_{10}$ and Nox with most convincing evidence for $PM_{2.5}$ pre- and post-natal exposures | NR | (141) |
| ASD | US EPA (2016) | $NO_2$, NO, Nox | Limited evidence based on only two studies | limited | (25) |
| ASD | US EPA (2019) | PMs | Generally increased risks based on five studies, limited evidence | limited | (17) |
| ASD | US EPA (2020) | Ozone | Some epidemiologic evidence to suggest that prenatal or early life exposure to ozone may increase the risk, based on five studies | limited | (23) |
| ASD | Lin (2022) | $PM_{2.5}$, $PM_{10}$ | Significantly elevated risks especially strong evidence for the association with $PM_{2.5}$ exposure in the first year of life and moderate evidence for prenatal exposure. Study quality on associations with $PM_{10}$ or other exposure windows very low or insufficient. | strong for prenatal $PM_{2.5}$, moderate | (140) |
| ASD | HEI (2022) | TRAP: $NO_2$, NOx, NO BC/EC, $PM_{2.5}$, $PM_{10}$, $PM_{10\text{-}2.5}$, proximity, PAH, benzene | Pre-natal or early life exposure to $NO_2$ and $PM_{2.5}$ showed generally increased risk with less evidence for other TRAP pollutants, based on 14 studies | NR | (99) |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 54: Characteristics of included reviews on autism spectrum disorder attributed to ambient air pollution**

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search up to | DB searched | Publication year range | Origin of studies (#) | Quality tool |
|---|---|---|---|---|---|---|---|---|---|
| ASD | Dutheil (2021) | $PM_{10}$, $PM_{2.5}$, Nox, metals, Ozone | yes | 28 | Jul 2020 | 4 | 2013-2020 | North America, Europe, Asia (1) | SIGN checklist (biases) |
| ASD | Lin (2022) | $PM_{2.5}$, $PM_{10}$ | yes | 31 | Jan 2022 | 5 | 2013-2022 | Europe, North America, Asia | GRADE, best evidence synthesis system |
| ASD | HEI (2022) | TRAP: $NO_2$, NOx, NO BC/EC, $PM_{2.5}$, $PM_{10}$, $PM_{10-2.5}$, proximity, PAH, benzene | no | 14 | Jul 2019 | 2 | 2011-2018 | NR | OHAT |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

## Table 55: Summary estimates from meta-analyses from selected reviews on autism spectrum disorder attributed to ambient air pollution

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric [HR, OR, RR] | Estimate | 95%-CI | Model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ASD | NOx pregnancy | Dutheil (2021) | 10 µg/m3 | 8 pessimistic model | OR | 0.99 | 0.97, 1.02 | NR | NR | NR | NR |
| ASD | NOx pregnancy | Dutheil (2021) | 10 µg/m3 | 8 optimistic model | OR | **1.04** | **1.00, 1.09** | NR | NR | NR | NR |
| ASD | NOx post-natal | Dutheil (2021) | 10 µg/m3 | 4 pessimistic model | OR | 1.02 | 0.97, 1.07 | NR | NR | NR | NR |
| ASD | NOx post-natal | Dutheil (2021) | 10 µg/m3 | 4 optimistic model | OR | 1.07 | 0.96, 1.18 | NR | NR | NR | NR |
| ASD | $PM_{2.5}$ entire pregnancy* | Lin (2022) | 10 µg/m3 | 13 | OR | **1.32** | **1.03, 1.69** | RE | 94% | 0.432 (egger) | no indication of publication bias |
| ASD | $PM_{2.5}$ 1st year | Lin (2022) | 10 µg/m3 | 9 | OR | **1.69** | **1.22, 2.15** | RE | 61% | **0.030 (egger)** | similar results after trim and fill |
| ASD | $PM_{2.5}$ 2nd year | Lin (2022) | 10 µg/m3 | 3 | OR | **3.13** | **1.47, 6.67** | RE | 0% | 0.351 (egger) | no indication of publication bias |
| ASD | $PM_{10}$ entire pregnancy | Lin (2022) | 10 µg/m3 | 10 | OR | 1.03 | 0.95, 1.11 | RE | 77% | 0.294 (egger) | no indication of publication bias |
| ASD | $PM_{10}$ 1st year | Lin (2022) | 10 µg/m3 | 6 | OR | **1.12** | **1.00, 1.26** | RE | 67% | 0.025 | NR |
| ASD | $PM_{10}$ | Lin (2022) | 10 µg/m3 | 0 | OR | 0.95 | 0.88, 1.01 | FE | 0% | 0.082 | NR |
| ASD | PMs | Zhang (2022) | no increment given | | | 1.11 | 0.93, 1.33 | | 60.10% | 0.014 | NR |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

*Reading example for the association of autism spectrum disorder with $PM_{2.5}$ exposure (Lin 2022): the risk of autism spectrum disorder is **significantly** increased by 32%, with a confidence range of the true effect between 3 and 69% for a 10 µg/m3 higher $PM_{2.5}$ exposure during pregnancy. Heterogeneity $I^2$ of study results was high, indicating high between study variation. Publication bias was not detected. Statistical significance (indicated as bold effect estimates) refers to the probability that the observed result could have occurred randomly if it has no true underlying effect. If an estimate is significant, such random occurrence is unlikely

### Attention-Deficit/Hyperactivity Disorder - ADD/ADHD

Attention-deficit disorder, with or without hyperactivity (ADD/ADHD) is marked by an ongoing pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development. ADHD is one of the most common *neurodevelopmental* disorders of childhood. Three reviews on ADHD, Lin et al. (140), Zhang et al. (142) and Donzelli et al. (143), as well as the HEI TRAP report (99) were included (see Table 56 to Table 58 below). Lin et al. (140) and Donzelli et al. (143) investigated the association between ADHD and particulates. While Lin et al. (140) included one more recently published study and conducted a meta-analysis, Donzelli et al. (143) included more studies (12 vs. 3), but did no quantitative analysis. Both studies assessed the level of evidence with either GRADE or the OHAT assessment tool. Zhang et al. was included for the analysis of NOx and PAHs. They conducted meta-analysis and found 5 studies on NOx and 3 on PAHs published between 2009 and 2019. The evidence level was not assessed. The HEI report (99) provided a qualitative assessment on 8 studies. Primary studies in the reviews were mainly conducted in North America and Europe.

Overall, results of epidemiological studies regarding associations of ambient air pollution with ADHD and related behaviors show mixed results. The number of studies is low and the inconsistent findings result in insufficient or low evidence ratings for an association with air pollution (140,143). This null association was also reported in a European study on ADHD symptoms in children from European birth cohorts (144), that was also included in the analysis of Zhang et al. (142). The qualitative literature review by the HEI panel concluded that there is low evidence of an association of TRAP with ADHD and related behaviors. Only the 2018 WHO report (19) reports on a growing literature. Currently, the evidence for an association of air pollution with ADHD and related behaviors is low.

**Table 56: Results of the included reviews on attention deficit (hyperactivity) disorder attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant(s) (focus) | Selected results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| ADHD | Lin (2022) | $PM_{2.5}$, $PM_{10}$ | Inconsistent evidence with high quality studies lacking | inconsistent | (140) |
| ADHD | Zhang (2022) | PM, Nox, PAH | Limited number of studies with low indication of increased risk | number is limited | (142) |
| ADHD | Donzelli (2019) | PMs | 6 out of 8 studies reported at least one statistically significant association with PM. | insufficient for causal association | (143) |
| ADHD | HEI (2022) | TRAP: $NO_2$, EC, $PM_{2.5}$, $PM_{10}$, $PM_{10-2.5}$, PAH, proximity | Limited study base. low confidence for an association of TRAP with ADHD and related behaviors. Most studies reported null associations. | low | (99) |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

### Table 57: Characteristics of included reviews on attention deficit (hyperactivity) disorder attributed to ambient air pollution

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search up to | DB searched | Publication year range | Origin of studies (#) | Quality tool |
|---|---|---|---|---|---|---|---|---|---|
| ADHD | Lin (2022) | $PM_{2.5}$, $PM_{10}$ | yes | 31 (20 in meta) | Jan 2022 | 5 | 2013-2021 | Europe, North America, Asia | GRADE, best evidence synthesis system |
| ADHD | Zhang (2022) | PM, NOx, PAH | yes | 9 | Jul 2019 | 3 | 2009-2019 | Europe, North America, Asia | NOS |
| ADHD | Donzelli (2019) | PMs | no | 12 | Dec 2018 | 2 | 2011-2018 | Europe, North America, Asia | NOS, OHAT |
| ADHD | HEI (2022) | TRAP: $NO_2$, EC, $PM_{2.5}$, $PM_{10}$, $PM_{10-2.5}$, PAH, proximity | no | 8 | Jul 2019 | 2 | 2013-2019 | NR | OHAT |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

### Table 58: Summary estimates from meta-analyses from selected reviews on attention deficit (hyperactivity) disorder attributed to ambient air pollution

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric [HR, OR, RR] | Estimate | 95%-CI | Model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ADHD | $PM_{10}$ | Lin (2022) | 10 µg/m3 | 3 | OR | 0.95 | 0.88, 1.01 | FE | 0% | 0.082 | too few studies |
| ADHD | PMs* | Zhang (2022) | no increment given | 6 | RR | 1.11 | 0.93-1.33 | NR | 60.10% | 0.014 | no indication of PB |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

*Reading example for the association of ADHD with particulate matter exposure (Zhang 2022): the risk of ADHD was not woth particulate matter exposure. The risk could be increased by 11%increased, but the confidence range of the true effect is between -7% (protective) and 33%. Heterogeneity $I^2$ of study results was moderate, indicating some between study variation. Publication bias was not detected.

### *Other outcomes affecting the nervous system*

#### Brain structure and development

Two reviews were included (see Table 59 to Table 61 below). Herting et al. (145) summarized 6 brain imaging MRI studies in children and young adults. Publications between 2015-2018 were assessed. Balboni et al. (146) reviewed hippocampal volume in adults and children in relation to air pollution. The hippocampus is a key brain structure that plays a role in neurodegeneration. 4 studies in children were included, of which 2 were meta-analytically combined. Both reviews, did not conduct formal risk of bias assessment.

Herting et al. (145) noted associations between exposure and brain, including: smaller white matter surface area (n = 1) and microstructure (n = 1); region-specific patterns of cortical thinness (n = 1) and smaller volumes and/or less density within the caudate (n = 3); altered resting-state functional connectivity (n = 2) and brain activity to sensory stimuli (n = 1). The authors conclude that the studies suggest an impact on MRI brain structure and function by air pollution. Effects seem to differ depending on exposure window and brain region. Thus, future air pollution-neuroimaging studies need to incorporate a developmental neurosciences perspective. Table 59 Herting et al. (145) highlighted stages of brain development t during the prenatal period (weeks) thru postnatal period of childhood and adolescence (years). This might explain results reported by Balboni et al. (146). While there was evidence for reduced hippocampal volume in adults with $PM_{2.5}$, no such association was found in children (146).

Overall, the study base is limited to jump to firm conclusions. However, based on few studies there seems suggestive evidence for an association of air pollution to changes to the brain structure that might influence brain function.

#### Depression / Anxiety

No reviews were available studying associations of depressive and anxiety symptoms or aggressive symptoms with air pollution in children. A study by Jorcano et al. (147) provided meta-analytically pooled data from 8 European birth cohorts, comprising over 13’000 children, studied at ages 7-11 years (see Table 59 to Table 61 below). Risks were slightly increased for aggressive symptoms in the borderline/clinical range with post-natal $NO_2$ exposure. Overall, the authors did not find evidence for an association between prenatal and postnatal exposure to several air pollutants and emotional and aggressive symptoms (Table 61).

#### Sleep Quality

One review by Liu et al. (148) looked into disturbed sleep quality in relation to air pollution across the life course (see Table 59 to Table 61 below). From 22 included papers, seven studied sleep health measures including sleep quality, sleep duration, sleep disturbances, and daytime sleepiness in children and adolescents, published between 2013-2019. Meta-analysis was not conducted. Study quality and evidence rating was assessed using methods that incorporated standards set by GRADE (149), OHAT (150) and the navigation guide (151). None of the children studies included populations from Europe.

Overall, there was some evidence that increased exposure to both ambient and indoor pollutants is associated with increased respiratory sleep problems and a variety of additional adverse sleep outcomes in children and adolescents. However, except for one study, all studies received a *low* evidence rating partly due to self-reported (unreliable) outcomes and lack of co-exposure assessments like noise. Except for respiratory related sleep disturbance plausible toxicological mechanisms remain inconclusive (148). The evidence base is limited and sleep quality in relation to air pollution have not been discussed as an outcome in the various UN reports consulted yet (19,21,93,105) .

**Table 59: Results of the included reviews on other nervous system effects attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant(s) (focus) | Selected results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| Brain imaging: Hippocampus | Balboni (2022) | PMs, Nos | Inconsistent results reported in two studies | NR | (146) |
| Brain Imaging, (cognitive function) | Herting (2019) | TRAP/PAH, EC, $NO_2$, metals, $PM_{10}$, $PM_{2.5}$, $PM_{10-2.5}$ | Few studies suggesting an impact on MRI brain structure and function by air pollution | NR | (145) |
| Sleep Quality | Liu (2020) | PM, Ozone, TRAP | some evidence that increased exposure to both ambient and indoor pollutants is associated with increased respiratory sleep problems and other adverse sleep outcomes | low | (148) |
| Depression, Anxiety, Aggression | Jorcano (2019) | PM2, Nos, $PM_{2.5}$abs, PAH | Slightly increased risks for aggressive symptoms in the borderline/clinical range with post-natal $NO_2$ exposure. Overall not evidence of an association | NR | (147) |
| Nervous system: behavior, cognitive function | US EPA (2010) | CO | Combined evidence from controlled human exposure and toxicological studies, the evidence is suggestive of a causal relationship between relevant short- and long-term exposures to CO and central nervous system effects. | suggestive | (32) |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 60: Characteristics of included reviews on other outcomes affecting the nervous system attributed to ambient air pollution**

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search up to | DB searched | Publication year range | Origin of studies (#) | Quality tools |
|---|---|---|---|---|---|---|---|---|---|
| Brain imaging: Hippocampus | Balboni (2022) | PMs, Nos | yes | 4 (2 children) | Jul 2021 | 2 | 2020-2021 | Europe 1, North America 1 | none |
| Brain Imaging, (cognitive function) | Herting (2019) | TRAP/PAH, EC, $NO_2$, metals, $PM_{10}$, $PM_{2.5}$, $PM_{10-2.5}$ | no | 6 | Sep 2018 | 2 | 2015-2018 | Europe, North America, South America | none |
| Sleep Quality | Liu (2020) | PM, Ozone, TRAP | no | 22 (7 children / adolescents) | Oct 2019 | 5 | 2010-2019 | Asia, North America, Europe other | Bamber 2019 |
| Depression, Anxiety, Aggression | Jocarno (2019) | PM2, Nos, $PM_{2.5}$abs, PAH | yes | 8 european cohorts | - | - | - | Europe | NR |
| Nervous system: behavioral abnormalities, learning and memory deficits, locomotor effects, neurotransmitter changes, and changes in the auditory system | US EPA (2010) | CO | no | | May 2009 | HERO database | - | - | Yes |

**Table 61: Summary estimates from meta-analyses from selected reviews and studies on other outcomes affecting the nervous system attributed to ambient air pollution**

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric [HR, OR, RR] | Estimate | 95%-CI | Model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| depressive and anxiety symptoms in borderline/clinical range | $NO_2$ prenatal | Jocarno (2019) | 10 µg/m3 | 13 | OR | 1.02 | 0.95, 1.10 | RE | 2.51% | 0.421 | - |
| depressive and anxiety symptoms in borderline/clinical range | $NO_2$ postnatal* | Jocarno (2019) | 10 µg/m3 | 9 | OR | 0.92 | 0.82, 1.03 | RE | 7.80% | 0.369 | - |
| aggressive symptoms in the borderline/clinical range | $NO_2$ prenatal | Jocarno (2019) | 10 µg/m3 | 13 | OR | 1.07 | 0.97, 1.19 | RE | 9.20% | 0.354 | - |
| aggressive symptoms in the borderline/clinical range | $NO_2$ postnatal | Jocarno (2019) | 10 µg/m3 | 9 | OR | 0.93 | 0.82, 1.06 | RE | 0.00% | 0.709 | - |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

*Reading example for the association of symptoms of depression and anxiety in the borderline/clinical range with $NO_2$ exposure (Jocarno 2019) the risk of symptoms was not associated with $NO_2$ exposure after birth. The risk could be decreased by 8%, but the confidence range of the true effect is between 18% decreased (protective) and 3% increased risk. Heterogeneity $I^2$ of study results was low, indicating low between study variation. In this pan-European study that pooled results from different cohorts in one study publication bias was not relevant.

### *Cardiometabolic effects*

#### Changes in glucose metabolism

Changes in glucose metabolism are early indicators of disturbed glucose metabolism that might lead to diabetes type 2 or metabolic syndrome. None of the included reviews were specific for children. However, two reviews included studies in children and adolescents (see Table 62 to Table 64 below). Dang et al (152) studied markers of insulin resistance with air pollution up to January 2018 and included four out of six studies from children / adolescents. These four studies were published between 2013-2018. Meta-analysis was conducted for $PM_{2.5}$, $PM_{10}$, and $NO_2$ including adult studies. Study quality was assessed with the Newcastle Ottawa Scale. The review on TRAP and metabolic dysfunction by Alderete et al. (153), including studies up to August 2017, dedicated a chapter on children studies including six studies published between 2013 and 2017. The review includes more studies even though it only searched one database and did not conduct quality assessment. The majority of studies included in the reviews was conducted in Europe or North America. The evidence base is supported by the ISAs on ozone (23), PM (17) and $NO_2$ (25).

Overall, epidemiological studies on metabolic effects in association with air pollution have only been published in the last 10 years, with emerging evidence on early perturbations already in children. Studies were mainly conducted in Europe and North America. The number of studies and evidence base is limited with no children studies reporting dose-response relationships. Associations are reported with various air pollutants and plausible biological mechanisms exist. Thus, we expect further evidence to strengthen the likely and suggestive ratings by the US EPA and believe the evidence for the time being to be low, but emerging.

**Table 62: Results of the included reviews on changes in glucose metabolism attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant (s) (focus) | Selected results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| Insulin Resistance | Dang (2018) | $PM_{2.5}$, $PM_{10}$, $NO_2$ | Evidence for an association of insulin resistance with $NO_2$ and particulates in children. Results with $PM_{2.5}$ not significant. | NR | (152) |
| Metabolic dysfunction, diabetes | Alderete (2018) | $NO_2$, $PM_{2.5}$, Nox, Proximity | Increased air pollution could affect the underlying pathophysiology of type 2 diabetes, including insulin resistance and β-cell dysfunction. | suggestive | (153) |
| Glucose homeostasis | US EPA (2019) | PMs | Limited but increasing number of epidemiological findings. Together with inconsistent findings from experimental studies. | suggestive | (17) |
| ST:glucose metabolic effects | US EPA (2020) | Ozone | Consistent evidence from experimental and epidemiological studies on metabolic effects with short-term exposure to air pollution. | likely to be causal | (23) |
| CVD, metabolic disease / diabetes | US EPA (2016) | $NO_2$, NO, NOx | Limited number of studies with no special mention of studies in children. Evidence is suggestive | suggestive | (25) |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 63: Characteristics of included reviews on changes in glucose metabolism attributed to ambient air pollution**

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search up to | DB searched | Publication year range | Origin of studies (#) | Quality-tool |
|---|---|---|---|---|---|---|---|---|---|
| Insulin Resistance | Dang (2018) | $PM_{2.5}$, $PM_{10}$, $NO_2$ | yes | 6, 4 on children | Jan 2018 | 8 | 2013-2018 | Europe (4), North America (2) | NOS |
| Metabolic dysfunction, diabetes | Alderete (2018) | $NO_2$, $PM_{2.5}$, Nox, Proximity | no | 6 on risk in children | Aug 2017 | 1 | children studies: 2013-2017 | North America (3), Europe (2), South America (1) | None |

**Table 64: Summary estimates from meta-analyses from selected reviews on changes in glucose metabolism attributed to ambient air pollution**

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric | Estimate | 95%-CI | Metaanalysis model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Insulin resistance: HOMA-IR | $PM_{2.5}$ | Dang (2018) | 1 µg/m3 | 6 | %-change | -0.26 | -1.06, 0.53 | FE | 43.60% | 0.091 | NR |
| Insulin Resistance: Insulin | $PM_{2.5}$ | Dang (2018) | 1 µg/m3 | 6 | %-change | 2.39 | -0.69, 5.46 | RE | 93.80% | 0.000 | NR |
| Insulin resistance: HOMA-IR | $NO_2$* | Dang (2018) | 1 µg/m3 | 5 | %-change | **1.25** | **0.69, 1.84** | FE | 0.00% | 0.071 | NR |
| Insulin Resistance: Insulin | $NO_2$ | Dang (2018) | 1 µg/m3 | 5 | %-change | **0.6** | **0.17, 1.03** | FE | 30.90% | 0.267 | NR |
| Insulin resistance: HOMA-IR | $PM_{10}$ | Dang (2018) | 1 µg/m3 | 5 | %-change | **2.77** | **0.67, 4.87** | RE | 95.00% | <0.0001 | Not detected |
| Insulin Resistance: Insulin | $PM_{10}$ | Dang (2018) | 1 µg/m3 | 4 | %-change | **2.75** | **0.45, 5.04** | FE | 58.70% | 0.057 | Not detected |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

*Reading example for the association of insulin resistance, measured as HOMA-IR, $NO_2$ exposure (Dang 2018): the measure for insulin resistance is **significantly** increased by 1.25%, with a confidence range of the true effect between 0.69 and 1.84% for a 10 µg/$m^3$ higher long-term $NO_2$ exposure. Heterogeneity $I^2$ of study results was low, indicating low between study variation. Publication bias was not assessed. Statistical significance (indicated as bold effect estimates) refers to the probability that the observed result could have occurred randomly if it has no true underlying effect. If an estimate is significant, such random occurrence is unlikely

### Overweight / Obesity

Four reviews have been included studying either obesity risk with air pollution or increases of BMI in association with air pollution, or both (see Table 65 to Table 67 below). Lin et al. (154) presented the most updated evidence for $PM_{10}$ and $PM_{2.5}$ associated with obesity in all age groups with separate results for the young. Studies were published 2014-2021. The OHAT and GRADE approach for quality assessment and evidence synthesis were used. The results for obesity were complemented by the reviews of Parasin et al. (155) for $PM_{2.5}$ absorbtion and $PM_{10-2.5}$ as well as the review by Huang et al. (156) presenting pooled results for $NO_2$ and Ozone including studies from 2001-2018 and 2017-2020, respectively. The former used the OHAT approach for quality assessment whereas the latter did not use a specific tool but conducted sensitivity analyses. Associations with body weight changes measured as BMI were studied by Huang et al. (156) presenting results for $PM_{2.5}$, $PM_{10}$, $NO_2$ as well as by Wang et al. (157) presenting results for traffic indicators and NOx. Wang et al. (157) used the OHAT approach for quality assessment and included studies published between 2001 to 2018. The majority of studies was conducted in Europe or North America.

Overall, there is some limited evidence for an association of air pollution with increased weight or risk of obesity in the young, especially for $NO_2$ and PM. The study base is limited and heterogeneity between studies is high. Lin et al. (154) conclude that the overall evidence is low. None of the included studies reported a dose-response gradient. To date, evidence for overall metabolic effects of PM or $NO_2$ is only suggestive according to the US EPA, lacking co-pollutant models and showing largely inconsistent findings in epidemiological studies despite plausible biological mechanisms (17,25). Therefore, the evidence base can be considered as low.

**Table 65: Results of the included reviews on overweight and obesity attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant(s) (focus) | Selected results | Evidence level | Reference |
|---|---|---|---|---|---|
| obesity: Obesity adults and children | Lin (2022) | PM 2.5 | Significantly increased risk of obesity in infants, children or adolescents with higher effect estimates with post-natal exposure. PM-related effects were more pronounced in children than in adults. | overall low | (154) |
| obesity, BMI | Huang (2022) | PMs, NOx, SOx, CO, $O_3$ | Significantly increased BMI and risk of obesity with $NO_2$, $PM_{2.5}$, $PM_{10}$ and PM1. Number of studies was hihgest for $NO_2$ with not indication of publication bias. | NR | (156) |
| obesity: BMI, BMI z-score, overweight/ obesity, weight related behaviors | Wang (2021) | traffic Nox and behaviors | Significantly elevated BMI with Nox exposure, but mixed results for traffic indicators | mixed results for traffic measures | (157) |
| obesity: BMI, BMI z-score, overweight/ obesity | Parasin (2021) | $PM_{10}$, $PM_{2.5}$, $PM_{10-2.5}$, $NO_2$, Nox, $PM_{2.5}$abs, NO | Obesity risk significantly increased with $PM_{2.5}$abs, based on 3 studies | NR | (155) |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 66: Characteristics of included reviews on overweight and obesity attributed to ambient air pollution**

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search date up to | DB searched | Publication year range | Origin of studies (#) | Quality tool |
|---|---|---|---|---|---|---|---|---|---|
| obesity: Obesity adults and children | Lin (2022) | PM 2.5 | yes | 13 | Jan 2022 | 5 | 2014-2021 | Europe (4), North America (2), Asia (7) | NTP-OHAT, GRADE |
| obesity, BMI | Huang (2022) | PMs, NOx, SOx, CO, $O_3$ | yes | 15 | dec 2021 | 4 | 2014-2021 | Europe (6), North America (3), Asia (6) | sensitivity analysis |
| obesity: BMI, BMI z-score, overweight/obesity, weight related behaviors | Wang (2021) | traffic Nox and behaviors | only Nox, traffic | 39: 26 traffic flow, 11 AirP: 3 for NOx | Jan 2019 | 4 | 2001-2018 all studies (no separate AirP results available) | Europe (14), North America (18), other (7) | National Institutes of Health's Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies |
| obesity: BMI, BMI z-score, overweight/obesity | Parasin (2021) | $PM_{10}$, $PM_{2.5}$, $PM_{10-2.5}$, $NO_2$, Nox, $PM_{2.5}$abs, NO | yes | 8 | Sep 2020 | 3 | 2014-2020 | Europe (5), Asia (3) | NOS, Cochrane RoB |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

## Table 67: Summary estimates from meta-analyses from selected reviews on overweight and obesity attributed to ambient air pollution

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric | Estimate | 95%-CI | Metaanalysis model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| obesity | PM 2.5 | Lin (2022) | 10 µg/m3 | 7 | OR | **1.242** | **1.093, 1.41** | RE | 99.50% | <0.001 | Asymmetry, trim-and-fill showed unaltered results |
| obesity | $PM_{10}$ | Lin (2022) | 10 µg/m3 | 7 | OR | **1.1** | **1.04, 1.16** | RE | 89.80% | <0.001 | Asymmetry, trim-and-fill showed unaltered results |
| obesity | $PM_{2.5}$ maternal | Lin (2022) | 10 µg/m3 | 5 | OR | **1.06** | **1.02, 1.11** | RE | 93.90% | 0.000 | NR |
| obesity | $NO_2$* | Huang (2022) | 10 µg/m3 | 11 | OR | **1.11** | **1.06, 1.18** | RE | 84.10% | <0.001 | no publication bias |
| obesity | PM1 | Huang (2022) | 10 µg/m3 | 3 | OR | **1.41** | **1.30, 1.53** | RE | 0.00% | 0.905 | no publication bias |
| obesity | Ozone | Huang (2022) | 10 µg/m3 | 2 | OR | 1.08 | 0.99, 1.18 | RE | 71.50% | 0.061 | no publication bias |
| BMI | $PM_{2.5}$ | Huang (2022) | 10 µg/m3 | 3 | beta | **0.11** | **0.05, 0.17** | RE | 82.60% | 0.003 | publication bias detected, no trim and fill |
| BMI | $PM_{10}$ | Huang (2022) | 10 µg/m3 | 3 | beta | **0.08** | **0.03, 0.12** | RE | 89.10% | <0.001 | publication bias detected, no trim and fill |
| BMI | $NO_2$ | Huang (2022) | 10 µg/m3 | 5 | beta | **0.03** | **0.01, 0.04** | RE | 48.60% | 0.100 | no publication bias |
| BMI | Traffic | Wang (2021) | NR | 2 | beta | 0 | 0.01 | RE | 86% | <0.001 | Not assessed, number to low |
| BMI | NOx | Wang (2021) | NR | 3 | beta | **0.05** | **0.00, 0.10** | RE | 89% | <0.01 | Not assessed, number to low |
| obesity | ($PM_{10-2.5}$) | Parasin (2021) | NR | 2 | OR | **1.07** | **0.95, 1.20** | RE | 0% | 0.530 | no publication bias |
| obesity | $PM_{2.5}$abs | Parasin (2021) | NR | 3 | OR | **1.23** | **1.06, 1.43** | RE | 0% | 0.850 | no publication bias |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

*Reading example for the association of obesity in children with $NO_2$ exposure (Huang 2022): the risk of obestiy is **significantly** increased by 11%, with a confidence range of the true effect between 6 and 18% for a 10 µg/m3 higher $NO_2$ exposure. Heterogeneity $I^2$ of study results was high, indicating high between study variation. Publication bias was not detected. Statistical significance (indicated as bold effect estimates) refers to the probability that the observed result could have occurred randomly if it has no true underlying effect. If an estimate is significant, such random occurrence is unlikely.

### Blood pressure

The review by Yan et al. (158) included 15 studies, published between 2014 and 2021, analyzing associations of blood pressure and hypertension risk in children and adolescents with short-term and long-term air pollution including meta-analyses for $PM_{10}$, $PM_{2.5}$ and $NO_2$. This was the most comprehensive review including meta-analysis using the JBI tool for quality assessment (see Table 68 to Table 70 below). Not quite half of the studies included in the review were conducted in Europe or North America.

Overall, there is some evidence linking air pollution to increased blood pressure and a possibly higher risk for hypertension in children and adolescents, especially with particulate matter pollution. The US EPA (17) rates the evidence for short- and long-term effects on cardiovascular health end-points of particulate matter as *causal*. Since changes leading to cardiovascular disease in adulthood start at young ages, effects might already start as early as childhood. However, according to the ISA studies of children did not support an association between long-term $PM_{2.5}$ exposure and blood pressure. Evidence for other pollutants is even less certain. The evidence for effects on blood pressure in children is low based on a limited number of studies but with possibly far reaching health consequences into adulthood.

**Table 68: Results of the included reviews on blood pressure attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant(s) (focus) | Selected results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| Blood pressure | US EPA (2019) | PMs | Evidence for short- and long-term effects on cardiovascular health end-points causal in adults, but such associations were not supported by children studies. | children studies did not support ass | (17) |
| Blood Pressure, Hypertension risk | Yan (2021) | LT & ST: $PM_{10}$, $PM_{2.5}$ PM1.0, $NO_2$, $SO_2$, $O_3$, CO | Long-term exposure was associated with increased blood pressure measures with more pronounced effects for $PM_{2.5}$ than $PM_{10}$. Short-term exposure to $PM_{10}$ also increased blood pressure. Only diastolic blood pressure was significantly increased with long-term $NO_2$ exposure. Limited number of ozone studies indicating possibly higher systolic blood pressure with long-term ozone. | | (158) |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 69: Characteristics of included reviews on blood pressure attributed to ambient air pollution**

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search date up to | DB searched | Publication year range | Origin of studies (#) | Quality-tool |
|---|---|---|---|---|---|---|---|---|---|
| Blood pressure | US EPA (2019) | PMs | no | NR | Feb 2015 | HERO database | NR | NR | yes |
| Blood Pressure, Hypertension risk | Yan (2021) | LT & ST: $PM_{10}$, $PM_{2.5}$ PM1.0, $NO_2$, $SO_2$, $O_3$, CO | yes | 15 | March 2021 | 4 | 2014-2021 | Other (8), Europe (6), North America (1) | JBI |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 70: Summary estimates from meta-analyses from selected reviews on blood pressure attributed to ambient air pollution**

| Outcome | Pollutant | First author (year) | Increment | # of studies or EE | Metric | Estimate | 95%-CI | Metaanalysis model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hypertension | LT: $PM_{10}$ | Yan (2021) | 10 µg/m3 | 4 | OR | **1.14** | **1.13, 1.21** | FE | 0% | 0.412 | no indication of publication bias |
| Systolic blood pressure | ST: $PM_{10}$ | Yan (2021) | 10 µg/m3 | 3 | mmHg | **0.26** | **0.00, 0.53** | RE | 97% | 0.000 | no indication of publication bias |
| Diastolic blood pressure | ST: $PM_{10}$ | Yan (2021) | 10 µg/m3 | 4 | mmHg | **0.32** | **0.19, 0.45** | RE | 86% | 0.000 | publication bias, trim-and-fill |
| Systolic blood pressure | LT: $PM_{2.5}$* | Yan (2021) | 10 µg/m3 | 8 | mmHg | **1.8** | **0.94, 2.65** | FE | 0% | 0.615 | no indication of publication bias |
| Diastolic blood pressure | LT: $PM_{2.5}$ | Yan (2021) | 10 µg/m3 | 9 | mmHg | **1.06** | **0.32, 1.80** | FE | 0% | 0.454 | no indication of publication bias |
| Systolic blood pressure | LT: $PM_{10}$ | Yan (2021) | 10 µg/m3 | 9 | mmHg | **0.5** | **0.19, 0.81** | RE | 82% | 0.000 | no indication of publication bias |
| Diastolic blood pressure | LT: $PM_{10}$ | Yan (2021) | 10 µg/m3 | 9 | mmHg | **0.34** | **0.11, 0.57** | RE | 79% | 0.000 | no indication of publication bias |
| Systolic blood pressure | LT: $NO_2$ | Yan (2021) | 10 µg/m3 | 5 | mmHg | 0.35 | -0.10, 0.79 | RE | 52% | 0.080 | no indication of publication bias |
| Diastolic blood pressure | LT: $NO_2$ | Yan (2021) | 10 µg/m3 | 5 | mmHg | **0.44** | **0.25, 0.63** | FE | 0% | 0.506 | no indication of publication bias |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

*Reading example for the association of systolic blood pressure with $PM_{2.5}$ exposure (Yan 2021): the systolic blood pressure is **significantly** increased by 1.8 mmHg, with a confidence range of the true effect between 0.94 and 2.65 mmHg for a 10 µg/$m^3$ higher long-term $PM_{2.5}$ exposure. Heterogeneity $I^2$ of study results was low, indicating low between study variation. Publication bias was detected and trim and fill did not alter the results. Statistical significance (indicated as bold effect estimates) refers to the probability that the observed result could have occurred randomly if it has no true underlying effect. If an estimate is significant, such random occurrence is unlikely.

***Leukemia***

Two reviews were included based on their recent search and comprehensiveness of pollutants and studies included (see Table 71 to Table 73 below). Wei et al (159) studied the association of ambient air pollution at with leukemia risk with a focus on different exposure windows from pregnancy to exposure at diagnosis. Twenty studies published between 1998 to 2020 were included. The Newcastle Ottawa Scale was applied for quality assessment. Meta-analysis was conducted for benzene, $NO_2$ and $PM_{2.5}$ exposure combining effect estimates from high vs. low air pollution. Additionally, dose-response analyses (160) were conducted for $NO_2$ and benzene. The results by Filippini et al. (161) were only included for the traffic density measures, since they included less studies on the same pollutants as in Wei et al. The Newcastle Ottawa Scale was applied for quality assessment (Table 72) and a combined dose-response analysis was conducted for traffic density measures.

Overall, there is some evidence on increased risk of childhood leukemia with ambient air pollution, specifically with traffic related indicators benzene and $NO_2$ showing both clear dose dependent monotonic increases of risk in the dose-response analysis (159,161). The majority of studies were conducted in Europe or North America. The association found with benzene is supported by IARC's classification of benzene to be a leukemogenin in adults for ALL (162). Though AML risks seemed to be higher in children than for ALL in relation to benzene exposure (Wei et al. 2021). The US EPA ISAs report few mixed results for $NO_2$ and $PM_{2.5}$. Both, the WHO Compendium (21) and the WHO report (19) list leukemia or childhood cancers in general as health effects, with the latter finding compelling evidence for an association. Due to the limited study base, the evidence for an association can be considered as moderate for childhood leukemia.

**Table 71: Results of the included reviews on leukemia attributed to ambient air pollution with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant(s) (focus) | Selected results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| Leukemia: ALL, AML | Wei (2021) | PM, Benzene, $NO_2$, Nox, windows of exposure | Studies indicating significantly increased leukemia risk with benzene and $NO_2$ exposure with linear-dose-response relationship. Associations with benzene more pronounced for AML-subtype, no differences observed for $NO_2$. Effect estimates for particulates non-significantly increased. | Clear dose-response relationship | (159) |
| Leukemia: ALL, ALM | Filippini (2019) | TRAP: indirect measures ($NO_2$, Benzene, PM) | Increased leukemia risk with higher traffic density. No difference between leukemia subtypes (ALL/AML) | Clear dose-response relationship, limited association | (161) |

T = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 72: Characteristics of included reviews on leukemia attributed to ambient air pollution**

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search date up to | DB searched | Publication year range | Origin of studies (#) | Quality-tool |
|---|---|---|---|---|---|---|---|---|---|
| Leukemia: ALL, AML | Wei (2021) | PM, Benzene, $NO_2$, Nox, windows of exposure | yes | 20 | Feb 2021 | 2 | 1998-2020 | Europe (12), North America (7), Asia (1) | NOS |
| Leukemia: ALL, ALM | Filippini (2019) | TRAP: indirect measures ($NO_2$, Benzene, PM) | yes | 29 | Mar 2019 | 3 | 1989-2018 | Europe (14), North America (13), Asia (2) | NOS |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

## Table 73: Summary estimates from meta-analyses from selected reviews on leukemia attributed to ambient air pollution

| Outcome | Pollutant | First author (year) | Increment of exposure [e.g. 10 µg/m³ categorial] | Metric [HR, OR, RR] | # studies or EE | Estimate | 95%-CI | Metaanalysis model [fixed / random-effect] | $I^2$ | p | Impact of PB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Leukemia | Benzene | Wei (2021) | 1 µg/m³ | RR | NR | 1.02 | 0.99, 1.05 | RE | NR | NR | NR |
| Leukemia | Benzene | Wei (2021) | high vs. Low | RR | 21 | **1.2** | **1.06, 1.35** | RE | 0.00% | 0.899 | publication bias detected, trim and fill attenuated results |
| ALL subtype | Benzene | Wei (2021) | high vs. low | RR | 11 | 1.07 | 0.95, 1.21 | RE | 0.00% | 0.899 | NR |
| AML subtype | Benzene* | Wei (2021) | high vs. low | RR | 10 | **1.61** | **1.30, 2.01** | RE | 0.00% | 0.899 | NR |
| Leukemia | $NO_2$ | Wei (2021) | 10 µg/m3 | RR | NR | **1.19** | **1.07, 1.32** | RE | NR | NR | NR |
| Leukemia | $NO_2$ | Wei (2021) | high vs. Low | RR | 27 | **1.04** | **1.02, 1.08** | RE | 25.70% | 0.112 | no indication of publication bias |
| ALL subtype | $NO_2$ | Wei (2021) | high vs. Low | RR | 13 | **1.07** | **1.02, 1.13** | RE | 25.70% | 0.112 | NR |
| AML subtype | $NO_2$ | Wei (2021) | high vs. Low | RR | 11 | **1.03** | **1.01, 1.06** | RE | 25.70% | 0.112 | NR |
| Leukemia | $PM_{2.5}$ | Wei (2021) | high vs. Low | RR | 12 | 1.03 | 0.98, 1.09 | RE | 30.90% | 0.144 | no indication of publication bias |
| Leukemia | Traffic density | Filippini (2019) | high vs. Low | RR | 16 | **1.09** | **1.00, 1.20** | RE | 56.20% | 0.012 | publication bias could not entirely be ruled out |

#=number, EE= effect estimate, metrics of effect: HR=hazard ratio, OR=odds ratio, RR= relative risk, CI= confidence interval, RE= random effects model, FE= fixed effects model, $I^2$= I-square; metric of heterogeneity, p= P-value, statistical metric, PB= publication bias, LT= long-term exposure, ST= short-term exposure, NR= not reported

* Reading example for the association of acute myeloid leukemia with benzene exposure (Wei 2021): the risk of AML was **significantly** increased by 61%, with a confidence range of the true effect between 30 and 201% comparing children with higher benzene exposure with children with lower benzene exposure. Heterogeneity $I^2$ of study results was low, indicating low between study variation. Publication bias was not assessed. Statistical significance (indicated as bold effect estimates) refers to the probability that the observed result could have occurred randomly if it has no true underlying effect. If an estimate is significant, such random occurrence is unlikely.

*Specific reviews on UFP exposure and children's health*

Two reviews were included summarizing health effects of exposure to ultrafine particles (UFP), that we were not able to integrate in the other chapters (see Table 74 and Table 75). Da Costa et al. (163) included 16 studies on children's health published between 2008-2018. Heinzerling et al. (164) focused on respiratory health effects in children and included 12 studies from 1997-2013 after searching one database only. None of the reviews conducted formal risk of bias assessment. Da Costa et al. (163) concluded that there was an association between children's health and exposure to UFPs, especially among children with respiratory diseases, who commonly experience alterations in inflammatory biomarkers and deterioration in lung function as a result of UFP exposure. Heinzerling et al. (164) reports on various respiratory effects associated with UFP exposure that were not robust in models including co-pollutants.

Overall, the evidence on health effects of UFP is emerging. The limited number of studies however prohibits firm conclusions.

**Table 74: Results of the included reviews on UFP exposure and children's health with evidence level according to authors (when available)**

| Outcome | First author (year) | Pollutant(s) (focus) | Selected results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|
| Children's health | da Costa (2019) | UFPs | Association of UFPs with health endpoints reported, especially respiratory health (inflammatory biomarkers, lung function) | NR | |
| Respiratory health | Heinzerling (2016) | UFPs | Associations with wheezing, asthma, lung function and asthma-related emergencies are reported. However, no significantly elevated risks in co-pollutant models. | evidence accumulating but inconclusive | |

T = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

**Table 75: Characteristics of included reviews on UFP exposure and children's health**

| Outcome | First author (year) | Pollutant(s) (focus) | Pooled results | # studies | search date up to | DB searched | Publication year range | Origin of studies (#) | Quality-tool |
|---|---|---|---|---|---|---|---|---|---|
| Children's health | da Costa (2019) | UFPs | no | 16 | Dec 18 | 3 | 2008-2018 | NR | none |
| Respiratory health | Heinzerling (2016) | UFPs | no | 12 | Feb 15 | 5 | 1997-2013 | Europe, North America, South America, Asia | none |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

### 3.1.5 Discussion

#### Main results

Ambient air pollution has severe health consequences for the unborn child, infants, children and adolescents. They are especially vulnerable due to their anatomical, physiological and behavioral differences to adults. We identified 73 individual reviews on specific health endpoints in children and adolescents including the integrated science assessments by the US EPA and the latest HEI review on health effects of long-term traffic related air pollution. Almost all reviews included studies conducted in Europe, integrating evidence from the European context into the results. In the wider air pollution research context, results from North American studies have generally been comparable to results from European studies. Since most reviews based their results on European and North American studies the results are highly relevant.

The systematic reviews showed **strong evidence** for health effects on mortality, respiratory endpoints such as development of asthma, decreased lung function and lung function development, and respiratory infections. Evidence from the systematic reviews was **moderate** for adverse birth outcomes such as preterm birth and low birth weight, development of leukemia, as well as adverse neurodevelopmental outcomes. Children exposed to ambient air pollution seem to be restricted in their cognitive development and to show structural changes in the brain and to be more likely to be diagnosed with autism. The evidence for an association with other outcomes was **lower**. For outcomes such as cardio-metabolic effects (blood pressure, glucose metabolism) evidence is emerging and a firm conclusion could not be drawn due to a limited number of studies or uncertainties regarding causal effects by single pollutants. Reduced birth weight, preterm birth, impaired lung function or neurocognitive development, diseases such as asthma can translate into weaker health in adulthood and can impair children's prospects for employment and to live a healthy, disease free life.

#### Magnitude of effects

The reported effect-estimates from the various meta-analyses are generally small. It can be observed that short-term effects are in general smaller than long-term effects (165). This can be attributed to the contribution of long-term exposure to sub-chronic and chronic disease increasing frailty in the population (166). In our umbrella review, we can only compare the effects of short-term vs. long-term exposure effects on blood pressure (effect of short-term $PM_{10}$ exposure on systolic blood pressure 0.26 mmHg vs. 0.5 mmHg of long-term exposure per 10 µg/m3, a duplication of the effect). Long-term effects of air pollution are also considerably of greater consequence when we consider that diminished lung-function growth, development of chronic respiratory disease and possibly a reduced or slowed cognitive development impairs the children's prospects in later life.

The effects shown might be small and negligible on an individual level. However, the public health impact of air pollution is considerable. Since air pollution affects the whole population, even a small increase of e.g. asthma risk by around 10% due to $NO_2$ (per 10 µg/m³ increased long-term exposure) in the children population is considerable. Also the small decreases of birth weight are of importance increasing the number of newborn experiencing complications due to low birth weight or preterm birth. Thus even though the effects are small for those effects with strong evidence it is clear that the disease burden in a population is shifted towards a more frail population.

#### Results in context to other reviews

Compared to reports by the WHO or other UN agencies and another umbrella review (38) our assessment is more cautious but generally falls in line with the listed health outcomes (Table 76). This might be attributed to a less rigorous assessment of the evidence level of reported outcomes. Indeed, formal confidence assessments have only recently been developed and applied to the field of environmental epidemiology.

Biological plausibility and mechanistic pathways of findings in epidemiological studies were not the focus of this umbrella review. We based most of our information on the integrated science assessment of the US EPA, which integrate information from toxicological, animal or experimental studies as additional lines of evidence in their causality ratings (167).

**Table 76: Evidence levels of health effects of ambient air pollution as reported in other reviews like UN reports compared to this assessment**

| Health Outcome | | Strength of Evidence | | | | | |
|---|---|---|---|---|---|---|---|
| | | **Rojas-Rueda** (38) | **WHO Compendium** (21) | **UNEP FAQ** (93) | **UNICEF key messages** (105) | **WHO 2018** (19) | **Our overall assessment 2022** |
| | Mortality | NR | listed | listed | listed | compelling evidence | strong |
| Birth outcomes | Low Birth weight / SGA | Moderate ($NO_2$, others low) | birth outcomes in general | listed | listed | strong evidence (low BW) PM | moderate |
| | Preterm Birth | Moderate (LT-$O_3$, others low) | birth outcomes in general | listed | listed | growing evidence | moderate |
| | SGA | low | birth outcomes in general | listed | listed | strong evidence (low BW) PM | moderate |
| | Intrauterine growth restriction | NR | birth outcomes in general | NR | NR | NR | low, based on limited number of studies |
| | Malformations | NR | NR | NR | NR | | very low, insufficient |
| Respiratory outcomes | Infections (ALRI/pneumonia / otitis media | Moderate | listed | listed | listed | robust / Compelling evidence PM | moderate - strong |
| | Lung function | NR | listed | child development in general | | robust / Compelling evidence | ST & LT strong |
| | Allergies | NR | NR | NR | NR | NR | ST exacerbation strong<br>LT low |
| | Asthma | Moderate (PM, EC, $NO_2$) | listed | | listed | substantial evidence | strong |
| | Asthma exacerbation | NR | | | listed | substantial evidence | strong |
| Neurologi | Neuro-development | NR | Brain development | child development in general | cognitive development | growing body of research | moderate, growing evidence |

| Health Outcome | | Strength of Evidence | | | | | |
|---|---|---|---|---|---|---|---|
| | | **Rojas-Rueda** (38) | **WHO Compendium** (21) | **UNEP FAQ** (93) | **UNICEF key messages** (105) | **WHO 2018** (19) | **Our overall assessment 2022** |
| | Autism | Moderate (PM) | NR | NR | NR | growing body of research | moderate, growing evidence |
| | ADD/ADHD | NR | NR | NR | NR | growing body of research | limited / low |
| | Brain structure | NR | NR | NR | NR | NR | Low, but suggestive based on limited number of studies |
| | Depression / Anxiety | NR | NR | NR | NR | NR | very low |
| | Sleep Quality | NR | NR | NR | NR | NR | very low |
| Cardio-metabolic | Glucose metabolism | NR | NR | NR | NR | NR | low, emerging evidence |
| | Overweight | NR | NR | NR | NR | NR | low, based on limited number of studies |
| | Blood pressure | NR | NR | NR | NR | NR | low but suggestive due to effects in adults |
| | Leukemia | NR | cancers | NR | listed | Childhood cancers: substantial evidence | moderate |

LT = long-term exposure, PMs= particulate matter of various sizes, NR = not reported, ST = short-term exposure.

***Methodological challenges***

We observed a variety of approaches for the assessment of evidence levels in the different reviews compiled. A basic quality assessment of included studies was found in the use of the Newcastle-Ottawa scale, which also considered some risk of bias. Approaches based on GRADE with rigorous risk of bias assessment and grading of the evidence have only been used lately and in a few reviews so far. It is important to note, that the confidence assessment and evidence synthesis might not be comparable across reviews. Even though the GRADE approach was used, certain adaptations might have influenced the end results of the assessments. For example, the original GRADE methodology starts rating results from observational studies per se as low evidence, which could be further downgraded or upgraded following the assessment. Once the evidence level is downgraded an upgrade is not possible. The methodology developed for the WHO Air Quality Guideline development modified the GRADE methodology and starts the evidence rating generated in cohort studies – the gold standard in epidemiological research – as moderate. Down- and upgrading the evidence is possible independent from each other (91,92). Thus, different ratings can results from different approaches, even though the evidence base is the same.

Except for two reviews on leukemia, we did not come across attempts to conduct an effects dose-response meta-analysis as described by Orisini et al. (160). Reviews, seldomly reported on exposure-response relationships. This might be due to the fact, that only few studies explore such relationships and thus pooling is not possible.

***Implications***

The new WHO Air Quality Guidelines (31) are set to protect all people including vulnerable populations such as children from adverse health effects. Indeed, in absence of thresholds for particulate matter air pollution and $NO_2$, the long-term Air Quality Guidelines are set at the lowest levels found in low level studies. Thus, implementing measures to achieve the proposed values of the Air Quality Guideline, will improve people's health tremendously, including the health of children. Legally binding limit values are important tools to guide air quality policy making. Such standards guide policy measures to achieve cleaner air. In 2017, less than ten countries followed the advice of WHO, setting standards in line with guidelines values from 2005 (113). The EU's limit values especially for particulate matter are much higher. Only 4% of the EU-population is exposed to particulate matter above the values defined in the EU-directive. However, 97% of the population is exposed to values considered harmful by the WHO (Figure 5).

### *3.1.6 Conclusion*

Ambient air pollution poses a risk for the health and well-being of children in Europe. The evidence is strong and convincing for various outcomes such as mortality, respiratory end-points and adverse birth outcomes. Evidence is less certain but emerging for other less studied health outcomes such as neurodevelopment or neurologic diseases in children and adolescents. In light of new evidence on health effects of low levels of exposure, the WHO has lowered its air quality guideline values to very low levels for particulate matter and $NO_2$, which apply to all people including children. In order to protect health of children in Europe exposure levels throughout Europe need to be reduced.

## 3.2 Indoor air pollution

In the sections below, the findings regarding secondhand smoke, formaldehyde and mould are explained. The search criteria are shown in Appendix A, the scanned references in Appendix B, and the detailed results of the screening in Appendix C.

### *3.2.1 Secondhand smoke (SHS)*

***Exposure risk characterization and overview of current exposure and impacts on children and adolescents in Europe***

Exposure to SHS is defined as the involuntary inhalation of cigarette smoke or smoke from other tobacco products. It is often also referred to as environmental tobacco smoke or passive smoke. SHS contains the same chemical substances as active smoke. Many of them have been classified as toxic or even carcinogenic for humans by the International Agency for Research on Cancer (IARC) (168,169).

About 31% of the European population is currently exposed to SHS in various places (170), about 12% of the children are regularly exposed to SHS at home (171). However, since the last two decades, tobacco smoke exposure in public places but also in private settings is decreasing significantly in many European countries. These declines are driven, among others, by the widespread ratification of the WHO Framework Convention on Tobacco Control, the EU Tobacco Products Directive and the implementation of national smoke-free legislation or other tobacco prevention policies (172). Though, there are differences in the development of SHS exposures between European countries. Ma et al. (173) examined the SHS exposure of adolescents between 1999 and 2018 and identified very different exposure trends, either decreasing, increasing or not changing, depending on the country. Country differences might be attributed to different smoking rates and levels of tobacco control policy actions (170,172). Also, the socioeconomic status can be a driving factor for SHS exposure at home. A study from Germany showed that socially disadvantaged children and adolescents were more likely to be exposed to SHS at home (59%) than children of parents with high socioeconomic status (21%) (174).

Of seven environmental risk factors studied, secondhand smoke following ambient air pollution was the risk factor contributing most to the burden of disease in children across Europe (7). There is also no safe

exposure level and health effects can be found at low exposure levels. Children are particularly vulnerable to SHS exposure before and after birth. Newborn babies and growing children have a higher breathing rate compared to adults and thus inhale larger amounts of harmful substances from cigarette smoke per kilogram bodyweight. Other influencing factors for higher susceptibility of children are the differences in metabolism compared to adults, their faster growth and the developing organ system (169). According to the 2019 Global Burden of Disease study (175), 2,323 deaths (95% CI: 1,428-3,313) among children younger than 15 years of age were linked to SHS exposure in the WHO European Region in 2019.

Health effects related to SHS exposure of children have been intensively investigated worldwide for many years. Long-term exposures have been shown to cause a variety of diseases or even death. The strongest evidence for a causal relationship with SHS exposure exists for low birth weight (LBW), asthma (ever), lower respiratory tract infections (LRI), impaired lung function, wheeze or shortness of breath, otitis media (OM) and sudden infant death syndrome (SIDS) (176–179). Besides these, there are indications for many other potential health effects. Parental smoking during pregnancy may furthermore impair the development of the unborn child or infant, e. g. increase the risk of miscarriage, preterm birth, small for gestational age or congenital malformations (38,176,180). In addition, both prenatal and postnatal exposure can also have negative effects later in childhood or even adulthood. This may include cognitive deficits or mental health problems. Even the development of cancer in children is suspected to be associated with SHS exposure, though controversially discussed in the literature. According to the Surgeon General's Report (176), there are indications of links with leukemia, brain tumors and lymphomas. In their umbrella review, Rojas-Rueda et al. (38) also mention a possible association of SHS exposure with neuroblastoma, but also attention-deficit hyperactive disorder (ADHD), obesity, neural tube defects and offspring depression.

For the health outcomes with strong evidence, several studies are available estimating or summarizing the burden of disease (BoD) from SHS exposure, both at the global level and for specific regions, such as Europe, or for individual countries (44,169,175,177,181). For example, Carreras et al. (171) quantified the mortality burden due to SHS exposure in children for different European countries in 2017. The results revealed that the highest number of attributable deaths and years of life lost (YLLs) were due to LBW, followed by LRI, asthma, SIDS and OM. Furthermore, the systematic review by Carreras et al. (44) on BoD studies related to SHS exposure also reported population attributable fractions (PAFs) of selected diseases for children in different European countries. Excerpts are shown in Table 77.

All findings highlight the need to pursue and expand efforts to minimize SHS exposure for children in a more targeted way to protect them from associated health risks.

**Table 77: Overview of PAF estimates for selected SHS-related outcomes for children in European countries, adopted from Carreras et al. (44)**

| Outcome | PAF range [%] | European country |
|---|---|---|
| Asthma induction (incidence) | 1.3-13.3 | Finland |
| | | The Netherlands |
| | | Poland |
| | | UK |
| LRI (incidence) | 10.6-20.9 | The Netherlands |
| | | Poland |
| | | UK |
| OM (incidence) | 7.1-15.4 | The Netherlands |
| | | Poland |
| | | UK |
| SIDS (mortality) | 19.6-22.4 | The Netherlands |
| | | Poland |
| | | UK |
| LBW (incidence) | 9.3 | Poland |

***Study search and selection***

The search for SHS was conducted in three databases on the 09th of May 2022. Because the PROSPERO database includes study protocols and no peer reviewed publications, only relevant articles mentioned in the protocols were selected in the search. Accordingly, these related articles were screened in the following review process. Overall and after removal of duplicates the literature search yielded 228 records (Figure 9). After the title and abstract screening 136 records were excluded. Hence, a total of 92 records was eligible for full text screening. Six additional publications were identified by hand search or expert knowledge, increasing the number of screened full texts to 98. A high number of records per outcome category was found in the subsequent literature screening process, in particular for asthma and other respiratory effects. This required stricter selection criteria (regarding timeliness and comprehensiveness of the systematic reviews or meta-analyses), leading to a total of 44 systematic reviews or meta-analyses for the umbrella review.

**Figure 9: PRISMA flow diagram for the search of selected health effects on children due to secondhand smoke. Search date 09 May 2022**

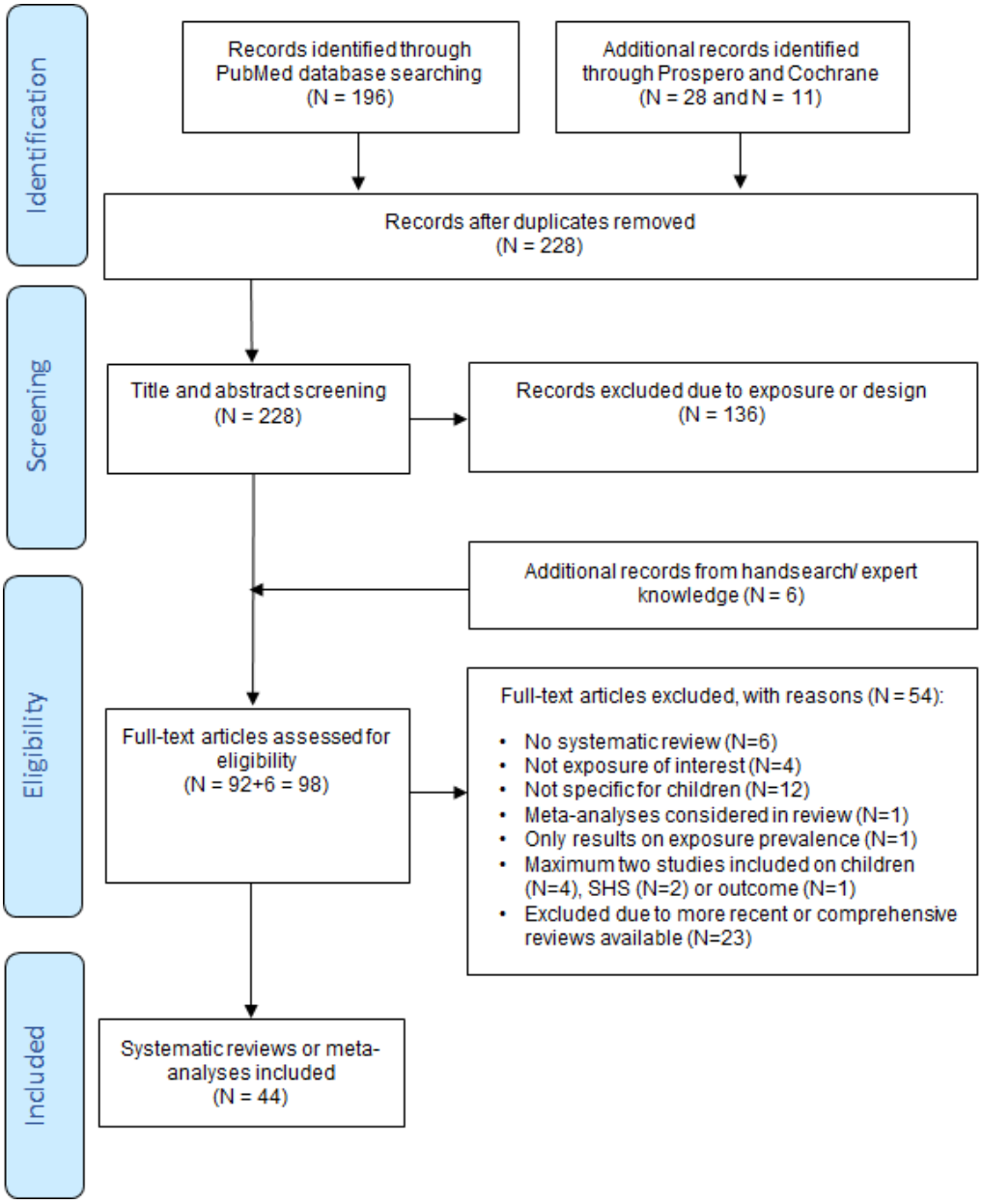


Table 78 lists all 23 systematic reviews or meta-analyses that were excluded due to the stricter selection criteria.

**Table 78: Excluded systematic reviews or meta-analyses due to more recent or comprehensive reviews available on secondhand smoke**

| Outcome category | Outcome | Excluded reference |
|---|---|---|
| Respiratory effects | Asthma development | Wang et al. (182) |
| | | Vardavas et al. (183) |
| | | Tinuoye et al. (184) |
| | | Burke et al. (185) |
| | | Ferrante et al. (186) |
| | | Silvestri et al. (187) |
| | | Dick et al. (188) |
| | Asthma attacks (hospitalization) | Dick et al. (188) |
| | | Ardura-Garcia et al. (189) |
| | LRI | Jackson et al. (190) |
| | Otitis media | Zhang et al. (191) |
| | Allergic rhinitis | Hur et al. (192) |
| | Allergic dermatitis | Kantor (193) |
| | IMD | Spyromitrou-Xioufi et al. (194) |
| | | Pilat et al. (195) |
| | Tuberculosis | Jafta et al. (196) |
| | Habitual snoring | Jara et al. (197) |
| Neurologic effects | Obstructive sleep apnoe | Jara et al. (197) |
| | Attention deficit hyperactivity disorder | Huang et al. (198) |
| Endocrine and metabolic effects | Overweight/obesity, BMI | Riedel et al. (199) |
| Birth outcomes and developmental effects | Congenital malformations | Leonardi-Bee et al. (200) |
| | Neural tube effects | Wang et al. (201) |
| | Miscarriage, abortion | Leonardi-Bee et al. (200) |
| | Perinatal death | Leonardi-Bee et al. (200) |
| | Sudden infant death syndrome | Röösli (202) |
| Others | Cavitated lesions of caries in teeth | Hanioka et al. (203) |

***Study characteristics and quality assessment***

In total, 44 publications investigating associations between SHS and health outcomes for children were eligible for the assessment. 36 (82%) of the identified systematic reviews included meta-analyses.

From all the included publications, six were published between 2011-2013, nine between 2014-2016, 18 between 2017-2019 and 11 between 2020 and May 2022. Eight reviews (18%) used one or two literature databases to find eligible publications, 21 (48%) used between three and five databases and 15 (34%) used even more than five. 38 reviews assessed the risk of bias, most commonly by using the Newcastle-Ottawa

Scale. Publication bias was assessed in 29 reviews. The number of studies included in the respective reviews ranged from four to 200 studies. In terms of the study population age, three publications were exceptionally included that investigated children or adolescents older than 18 years of age (young adults up to 25 years) (204–206).

***Health outcomes and evidence***

The finally considered 44 systematic reviews or meta-analyses reported 44 different diseases or causes of death for children or adolescents associated with SHS exposure. Most of them examined respiratory effects, birth outcomes or developmental effects, followed by neurologic, endocrine and metabolic effects as well as malignant neoplasms and a residual category named other outcomes (Table 79).

**Table 79: Number of identified outcomes and publications in the umbrella review on secondhand smoke**

| Outcome category | Number of outcomes | Number of systematic reviews/ meta-analyses |
|---|---|---|
| Respiratory effects | 15 | 14 |
| Birth outcomes and developmental effects | 10 | 10 |
| Neurologic effects | 4 | 5 |
| Endocrine and metabolic effects | 4 | 4 |
| Malignant neoplasms | 2 | 2 |
| Others | 9 | 9 |
| **Total** | **44** | **44** |

26 of the identified main outcomes were considered in only one systematic review or meta-analysis. Due to the stricter selection criteria favoring more recent and comprehensive reviews, 16 additional outcomes were considered by one systematic review or meta-analysis only. Exceptions were the outcomes LRI, allergic rhinitis and ADHD. LRI was evaluated by two included reviews as they differed in the consideration between mortality and morbidity. Two reviews on allergic rhinitis as well as on ADHD examined different exposure times (prenatal or postnatal), respectively.

Most of the review analyses generally assessed health differences between SHS exposed and unexposed population groups. In almost all identified systematic reviews or meta-analyses, SHS exposure assessment was based on self-reported information from questionnaires or interviews by parents or guardians. The exposure was mostly described qualitatively as a general exposure at home. Often, differentiation was made according to the person smoking in the household, e.g. the mother, the father or both parents. Many of the reviews also investigated different exposure time windows and differentiated between active or passive pre- and postnatal exposure, especially focusing on maternal influences. Some of the systematic reviews or meta-analyses reported on study results that were additionally based on quantitative exposure measures, such as the number of cigarettes smoked or measured concentrations of biomarkers (e.g. cotinine) in blood or urine. However, pooled evaluations for these exposure types were rarely carried out in the meta-analyses, as the exposure measurements in the individual studies were often too different. Studies reporting health outcomes based on interviews with adults on their SHS exposure during childhood were not considered in this umbrella review but are listed in Section 3.2.1 and in Appendix B.

An overview of the systematic reviews' or meta-analyses' characteristics and pooled effect estimates where available can be found in Appendix C.

### Respiratory effects

15 different respiratory health effects were reported in 14 systematic reviews (including ten meta-analyses) between 2011 and 2021 (Table 80). Eight reviews assessed prenatal maternal exposure (seven on active smoking, one on passive smoking, one on both), nine postnatal exposure (household, mother father, parents, others) and six evaluated both time periods. Four reviews examined (additionally) overall SHS exposure and did not differentiate between prenatal and postnatal exposure.

**Table 80:: Summary table on respiratory effects attributed to secondhand smoke**

| Outcome | First author (year) | Population/ age group | Exposure time not differentiated | Exposure prenatal | Exposure postnatal | Main results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|---|---|---|
| Allergic rhinitis | Saulyte (2014) | Children/ adolescents | Overall | Mother (active smoking) | | Significantly increased risk of allergic rhinitis after postnatal SHS exposure, whereas maternal smoking during pregnancy was not significantly associated with an increased risk. | Suggestive | (207) |
| Allergic rhinitis | Zhou (2021) | ≤18 years | | Mother (active smoking and passive smoking) | | Significantly increased risk of allergic rhinitis after prenatal SHS exposure, especially for maternal SHS exposure during pregnancy, whereas maternal active smoking during pregnancy was only significantly associated with an increased risk in subgroup analyses (study design: cross-sectional, region: America). | NR | (208) |
| Atopic dermatitis | Saulyte (2014) | Children/ adolescents | Overall | Mother (active smoking) | | Significantly increased risk of allergic dermatitis after SHS exposure, whereas maternal smoking during pregnancy was not significantly associated with an increased risk. | Suggestive | (207) |
| Food allergy | Saulyte (2014) | Children/ infants | Overall | Mother (active smoking) | | No significantly increased risk of food allergy after SHS exposure, but risk was significant in sub-analysis (study design cohort studies). Maternal smoking during pregnancy was not significantly associated with an increased risk. | Suggestive | (207) |
| Allergic sensitation | Feleszko (2014) | <18 years | | | Parents | Significantly increased risk of atopic sensitation after postnatal SHS exposure | NR | (209) |
| Asthma attacks/ exacerbation | Buelo (2018) | 5-12 years | Overall | | | Not entirely consistent results for SHS on asthma attacks, though there is high confidence that SHS exposure was associated with a slightly increased risk of an asthma attack | Highly confident | (210) |

| Outcome | First author (year) | Population/ age group | Exposure time not differentiated | Exposure prenatal | Exposure postnatal | Main results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|---|---|---|
| Asthma, Wheeze | He (2020) | <18 years | | Mother (active smoking) | Mother, father, household | Significantly increased risk of doctor-diagnosed asthma, wheezing and asthma-like syndrome after any type of SHS exposure, though higher OR were shown after prenatal maternal exposure | Considerable | (211) |
| Influenza (hospital/intensive care unit admissions) | Han (2019) | ≤15 years | | | Household | SHS exposure increased the risk of influenza-associated hospital admissions | Poor | (212) |
| Invasive meningococcal disease | Murray (2012) | <18 years | | Mother (active smoking) | Mother, father, parents, household | SHS exposure, and particularly maternal smoking during pregnancy, significantly increases the risk of invasive meningococcal disease | Some, growing evidence | (213) |
| LRI morbidity | Jones (2011) | <2 years | | Mother (active smoking) | Mother, father, parents, household | SHS by either parent or other household members significantly increased the risk of LRI, especially in the case of smoking mothers. Prenatal smoking had a weaker but still significant effect compared to postnatal smoking exposure. | NR | (214) |
| LRI mortality | Sonego (2015) | <5 years | Overall | | | SHS significantly increased LRI mortality. However, after removing the studies with high risk of bias, the effect estimate lost statistical significance. | NR | (215) |
| Otitis media (also called middle ear disease/infection) | Jones (2012) | Children | | Mother (active smoking) | Mother, father, household | SHS exposure, particularly due to mothers smoking, significantly increases the risk of middle ear disease | NR | (216) |
| Respiratory syncytial virus, bronchiolitis, or LRTI attributable to RSV or bronchiolitis | DiFranza (2012) | <5 years | | Mother (active smoking) | Mother, father, household | SHS exposure increases the risk of hospitalization for RSV-attributable lower respiratory tract infection and increases the severity of illness among hospitalized children | Ample evidence | |
| (Rhino)sinusitis | Hur (2014) | <18 years | Overall | | | Most of the included studies found a significant association between (rhino)sinusitis and SHS | Low | (217) |
| Tuberculosis | Patra (2015) | ≤15 years | | | Parents, household, other people | SHS exposure significantly increased the risk for tuberculosis in children | Not sufficient | (218) |
| Habitual snoring | Sun (2018) | Children | | Mother (active smoking) | Mother, father, household | Significantly increased risk for habitual snoring after any type of SHS exposure. | NR | (219) |

| Outcome | First author (year) | Population/ age group | Exposure time not differentiated | Exposure prenatal | Exposure postnatal | Main results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Strongest effects were reported for children who were exposed to maternal smoking (prenatal and postnatal). | | |

Notes: NR = not reported

### Allergies

Three meta-analyses were included, assessing the relationship between SHS exposure and allergic rhinitis, atopic dermatitis, food allergy or allergic sensitization. The reviews were of good quality using at least two literature databases and the Newcastle-Ottawa Scale, the Cochrane risk of bias tool or the Agency for Healthcare Research and Quality's checklist for study quality assessment. Only the review by Han et al. (212) did not assess study quality.

Allergic rhinitis was studied in the meta-analysis by Saulyte et al. (207). Since this publication also included studies on adult and active smoking, only the subgroup results for children/adolescents and SHS were extracted, in total 53 studies published between 1994-2012. The authors reported a significant association of allergic rhinitis with overall SHS (not differentiated by exposure time). Another more recent meta-analysis by Hur et al. (192) was available on the risk of sinusitis, though excluded during the full text screening because only nine studies on children were evaluated. Saulyte et al. (207) also assessed the association between maternal smoking during pregnancy and health effects pooling effect estimates of eleven studies. However, the more recent meta-analysis by Zhou et al. (208) on the same outcome considered 16 studies on prenatal SHS exposure published between 1997-2020 and was preferred in our analysis. They found a significant correlation between prenatal SHS exposure and allergic rhinitis, especially with respect to maternal SHS exposure during pregnancy. In contrast, findings for active maternal smoking during pregnancy were inconsistent as a significantly increased risk of allergic rhinitis was only identified in subgroup analyses on cross-sectional studies and studies performed in the US. Overall, Saulyte et al. (207) rated the level of **evidence as rather suggestive**.

Atopic dermatitis and food allergy were also studied by Saulyte et al. (207), evaluating the same SHS exposure specifications as described for allergic rhinitis. Evaluating 53 and six studies respectively, overall SHS exposure was associated with a significant risk increase for atopic dermatitis, though, the risk for food allergy was only increased when (five) cohort studies were analyzed. Maternal smoking during pregnancy, however, was not associated with both outcomes, examining 19 and three studies, respectively. The more recent meta-analysis by Kantor et al. (193) assessed the risk of atopic dermatitis in children and adults associated with active and passive smoking. However, this publication was excluded as the number of studies regarding the respective subgroups could not be differentiated. Overall, Saulyte et al. (207) rated the level of **evidence as rather suggestive**

Another meta-analysis on allergic sensitation from Feleszko et al. (209) was included. Pooled results of 24 studies published between 1988-2012 were reported, focusing on parental/household postnatal SHS exposure. The analysis indicated that SHS exposure significantly increases the risk of allergic sensitation in children, especially for preschoolers younger than seven years. However, the level of **evidence was not assessed** by the study authors. The Surgeon General's Report (176) rated the **evidence as inadequate**.

Overall, the research results **added evidence** especially on the relationship between overall and postnatal SHS exposure and allergic disease. Adverse effects due to prenatal maternal exposure were less consistent. However, it should be considered that the reported (lacking) associations might be biased as parents of children with allergic diseases may skew the results by avoiding smoking.

### Asthma

Athma development and asthma exacerbations due to SHS exposure have been frequently studied in the past. Eleven publications were identified on these two outcomes (Table 80). However, only the most recent or most comprehensive review was finally included in this umbrella review and described in the following: for asthma development the meta-analysis by He et al. (211) and for severe asthma attacks the systematic review by Buelo et al (210). Both publications were of good quality using at least two literature databases and the Newcastle-Ottawa Scale for study quality assessment.

He et al. (211) explored doctor-diagnosed asthma, asthma-like symptoms, and wheezing in relation to prenatal (maternal) as well as to postnatal (maternal, paternal, household) SHS exposure, including 93 studies published between 1990-2020. The analyses indicated **considerable evidence** that all types of SHS exposure were positively associated with all three outcomes. The association was strongest when related to prenatal maternal smoking. However, all analyses showed a high degree of heterogeneity. The Surgeon General's Report (220) assessed in 2014 the **evidence** to be **suggestive** for onset asthma and **sufficient** for wheeze, while the umbrella review by Rojas-Rueda (38) in 2021 rated the **evidence for asthma to be low**.

The systematic review by Buelo et al. (210) evaluated different risk factors associated with severe asthma attacks or asthma exacerbation in asthmatic children, including eight studies on SHS exposure published between 1993-2012. The results of the different studies varied. However, based on five studies reporting a significant association, the authors concluded a slightly increased risk of acute asthma attacks after overall SHS exposure. An expert panel evaluated the **evidence as highly confident**.

There is **profound evidence** for the development of childhood asthma and severe asthma attacks after SHS exposure. Nevertheless, it must be considered that the heterogeneity between the studies examined was very high, weakening the overall strength of evidence.

### Infections

Eight systematic reviews or meta-analyses reported on associations between SHS exposure and LRI (mortality and morbidity), respiratory syncytial virus (RSV), otitis media (also called middle ear disease/infection), influenza, (rhino)sinusitis, invasive meningococcal disease (IMD) or tuberculosis. The reviews were of good quality using at least two literature databases and the Newcastle-Ottawa Scale, the Cochrane risk of bias tool or the quality in prognosis studies tool for study quality assessment.

LRI was studied in two meta-analyses. Jones et al. (214) analyzed LRI morbidity including pneumonia, bronchitis, bronchiolitis or acute respiratory infection linked to prenatal (mother) as well as to postnatal (mother, father, household) SHS exposure in children under two years of age. The authors updated the meta-analysis by Strachan and Cook (221) and included in total 60 individual studies published between 1997-2010. They found that any type of SHS exposure significantly increased the LRI risk. The impact was strongest in relation to maternal smoking and weaker due to prenatal smoking. Another more recent meta-analysis by Jackson et al. (190) was also available but not considered in the umbrella review as fewer studies were included in this review. Sonego et al. (215), on the other hand, studied different risk factors for acute LRI mortality in children under five years of age in low- and middle-income countries. They included eight studies on overall SHS exposure (no publication period reported). The analysis indicated that SHS exposure significantly increases the risk of acute LRI mortality. After removing the studies with high risk of bias, the effect estimate was no longer statistically significant. The respective level of evidence was not assessed by the respective study authors. In general, the Surgeon General's Report (220) rated the association with SHS exposure as **sufficient evidence**.

In further relation to LRI, the systematic review by DiFranza et al. (222) investigated prenatal (mother) and postnatal (mother, father, household) SHS exposure as a risk factor for RSV, bronchiolitis, or hospitalization for LRI attributable to RSV or bronchiolitis among children under five years of age. The authors included 30 studies published between 1990-2009. Overall, the analysis found **ample evidence** for a positive association between SHS exposure and the risk of hospitalization for RSV-attributable LRI as well as increased disease severity among hospitalized children.

The risk of middle ear disease including OM in children associated with prenatal (mother) and postnatal (mother, father, household) SHS exposure was explored in the meta-analysis by Jones et al. (190). The authors updated the meta-analysis by Strachan and Cook (223) and included in total 61 individual studies published between 1978-2010. This study showed that particularly postnatal maternal, but also household SHS exposure significantly increases the overall risk of middle ear diseases among children and was most pronounced for middle ear disease cases requiring surgery. In addition, the authors used their results to calculate the share of middle ear disease cases in children up to the age of 15 years attributable to household SHS exposure in England 2007 (PAF), resulting in 7.5% of cases attributable to SHS exposure. Another more recent meta-analysis by Zhang et al. (191) was available on the risk of OM, though excluded during the full text screening because fewer studies and disease outcomes were evaluated. Overall, the level of **evidence was not assessed** by the study authors. Yet, the Surgeon General's Report (220)rated the association with SHS exposure as **sufficient evidence**. The umbrella review by Rojas-Rueda (38), on the other hand, assessed the strength of **evidence for OM as low**.

The systematic review by Han et al. (212) evaluated hospital or intensive care unit (ICU) admissions and deaths because of influenza in both active and passive smokers. Subgroup analyses for children included four studies on hospital or ICU admissions published between 2009-2017. Because of the low number of studies, a meta-analysis was not performed. Three out of four studies observed that SHS household exposure posed a higher risk of hospital or ICU admissions due to influenza infection in children younger than 15 years. Due to only limited available data, the authors evaluate the overall **evidence as poor**.

One systematic review explored the role of overall SHS exposure on (rhino)sinusitis in children and adults (217). Findings for children were based on nine studies published between 1988-2007. Six of the studies reported a significant association between (rhino)sinusitis and SHS exposure. Nevertheless, the authors rated the **evidence to be rather low**.

Murray et al. (213) conducted a meta-analysis on prenatal (mother) and postnatal (mother, father, parents, household) SHS exposure in relation to IMD in children or adolescents. The analysis included 17 studies, published between 1988-2006. The results indicated that both postnatal maternal, parental and household SHS exposure and particularly maternal smoking during pregnancy strongly increases the risk of IMD in children under 16 and even more in children under five years of age. The study authors derived s**ome, growing evidence** from the results. Two other more recent meta-analyses on this relationship were available (194,195). However, both publications were excluded as both included only three or four studies, respectively. Pilat et al. (195) assessed a mixed population including young adults up to 24 years of age. In contrast to the results of Murray et al. (213), the Surgeon General's Report concludes that there is **no causal relationship** between IMD and SHS exposure (176). Higher risk of IMD is assumed to be rather associated with increased risk of acquiring meningococcal bacteria among active smokers and an increased transmission to their contact persons. Direct effects of SHS exposure on IMD susceptibility are highly questionable (195).

Latent tuberculosis infection as well as acute tuberculosis in children and adults in relation to postnatal (parent, household, other people) SHS exposure was studied by Patra et al. (218). Subgroup results for children were based on 12 studies published between 1996-2014. The overall findings suggest that household SHS exposure significantly increases the risk of latent tuberculosis infection and even stronger increases were observed for acute tuberculosis, especially in children under five years of age. However, due to high heterogeneity between the studies, the **evidence is insufficient** to confirm an association. Also the Surgeon General's Report (220) rated the association with SHS exposure as **inadequate evidence** A similar meta-analysis by Jafta et al. (196) was not considered in this umbrella review as the authors evaluated eight studies, which were all included in the meta-analysis by Patra et al. (218). However, for this risk-outcome pair, it must be pointed out that SHS exposure increases the susceptibility to infection by the tuberculosis bacterium, which can possibly lead to active tuberculosis, rather than triggering tuberculosis directly.

All reviews reported at least one analysis with a significant association for each of the outcomes investigated. For LRI (morbidity) as well as for middle ear disease (and IMD), a greater influence of the

smoking mother was highlighted. The evidence for an association between passive smoking and influenza as well as (rhino)sinusitis (and tuberculosis) was assessed as low by the respective reviews.

#### Others

The meta-analysis by Sun et al. (219) explored habitual snoring in children, an early symptom of obstructive sleep apnoea, associated with prenatal (maternal) and postnatal (mother, father, household) SHS exposure. The analysis included 24 studies published between 1989-2017. Study results revealed a significantly increased risk of habitual snoring associated with any type of SHS exposure. The strongest impacts were found for children exposed to prenatal or postnatal maternal smoking. A previous systematic review on sleep disordered breathing including habitual snoring by Jara et al. (197) was not considered due to the lower number of studies evaluated. The level of **evidence was not assessed** by the study authors.

### Birth outcomes and developmental effects

Ten different birth outcomes or developmental effects were reported in ten meta-analyses. All meta-analyses assessed prenatal maternal exposure (eight on active smoking, six on passive smoking, four on both). Only one meta-analysis also reported associations with postnatal maternal exposure. Both prenatal and postnatal SHS exposure was linked to significantly increased risks of all birth outcomes. However, there were differences, if the mother smoked during pregnancy or was exposed to passive smoke herself (Table 81).

**Table 81: Summary table on all birth outcomes and developmental effects attributed to secondhand smoke**

| Outcome | First author (year) | Population/ age group | Exposure prenatal | Exposure postnatal | Main results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|---|---|
| Congenital heart defects | Zhao (2020) | Offspring | Mother (active and passive smoking), father (active smoking) | | Significantly increased congenital heart defects risk with all types of parental smoke exposure. | NR | (224) |
| Congenital malformations | Zheng (2019) | Offspring | Mother (passive smoking) | | Significantly increased risk for overall and several organ-system malformations with SHS exposure. Though, high heterogeneity and small study number for several organ-system malformations. | NR | (225) |
| Cryptorchidism | Yu (2019) | Infant (male) | Mother | | Significantly increased risk of delivering infants with cryptorchidism with prenatal maternal exposure. Note: results were | Sufficient evidence | (226) |

| Outcome | First author (year) | Population/ age group | Exposure prenatal | Exposure postnatal | Main results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|---|---|
| | | | | | based on crude effect measures. | | |
| Neural tube effects | Meng (2018) | Infant | Mother (active and passive smoking) | | Significantly increased risk of neural tube effect with passive smoking, but not with active smoking. | NR | (227) |
| Oral clefts | Xuan (2016) | Offspring | Mother | | Significantly moderately increased risk of oral clefts with SHS exposure | NR | (228) |
| Fetal measurements | Abraham (2017) | Fetus | Mother | | Significantly reduced fetal measurements after the first trimester, particularly reduced head size and femur length. | NR | (229) |
| Miscarriage | Pineles (2014) | Fetus | Mother (active and passive smoking during pregnancy, any active smoking in life) | | Significantly increased risk of miscarriage for active smoking (any time and during pregnancy), whereas passive smoking was not significantly associated with an increased risk. | Strengthened evidence | (230) |
| Perinatal death | Pineles (2016) | Fetus/ neonate | Mother (active and passive smoking) | | Significantly increased risk of perinatal death for active smoking (any time and during pregnancy) as well as passive smoking during pregnancy | Strengthened evidence | (231) |
| Sudden infant death syndrome | Zhang (2013) | <1 year | Mother | Mother | Both prenatal and postnatal smoking were associated with significantly increased risk of sudden infant death syndrome | NR | (232) |
| Preterm birth | Cui (2016) | Neonate | Mother (passive smoking) | | Significantly increased risk of preterm birth with SHS exposure | NR | (233) |

Notes: NR = not reported

### Congenital malformations or defects

Five meta-analyses were included reporting on associations of SHS exposure with congenital malformations, congenital heart defects, cryptorchidism, oral clefts or neural tube effects. All analyses were of high quality, using the Newcastle-Ottawa Scale for study quality assessment, except for Xuan et al. (228), who did not assess study quality, and included at least three databases in their systematic review.

The risk of congenital malformations in the offspring associated with prenatal maternal SHS exposure was explored in the meta-analysis by Zheng et al. (225). Malformations were grouped by organ system: nervous system; eye, ear, neck and face; cardiovascular system; respiratory system; oral clefts; urinary system and musculoskeletal system. The authors analyzed 33 studies published between 1996-2016. The results showed that passive maternal smoking increased the overall risk for malformations and specifically for nervous system and cardiovascular system malformations as well as for oral clefts. Malformations of the digestive system were also positively associated, though based on two pooled studies only. Due to the small number of studies on several organ-system malformations as well as high heterogeneity between the studies, the findings should be interpreted with caution. The level of **evidence was not assessed** by the study authors.

Xuan et al. (228) assessed the role of prenatal maternal smoking for the occurrence of oral clefts in the offspring. The meta-analysis included 29 studies published between 1974-2011. The results indicated that maternal active smoking during or shortly before pregnancy moderately increases the risk of oral clefts in the offspring. Yet, studies on a dose-response relationship remained inconsistent. The heterogeneity of the studies was low to moderate. The level of **evidence was not assessed** by the study authors. Yet, the Surgeon General's Report (220) rated the association with SHS exposure as sufficient **evidence.**

One meta-analysis by Zhao et al. (224) investigated congenital heart defects in the offspring in relation to maternal (active and passive) and paternal (active) smoking during pregnancy. Total heart defects as well as specific subtypes were explored, including atrial septal defect, atrioventricular septal defect, conotruncal heart defect, left ventricular outflow tract obstruction, right ventricular outflow tract obstruction, septal defect, transposition of the great arteries, tetralogy of fallot and ventricular septal defect. In total, 125 studies published between 1971-2018 were included. The authors found that maternal active and passive smoking as well as paternal active smoking before or during pregnancy was significantly associated with an increased risk of overall congenital heart defects in the offspring. Regarding subtype analyses, maternal active smoking was significantly linked to atrial septal defect and right ventricular outflow tract obstruction. However, due to substantial heterogeneity and potential bias the overall results should be evaluated with caution. The level of **evidence was not assessed** by the study authors. Yet, the Surgeon General's Report (220) rated the association with maternal prenatal smoking as **suggestive evidence.**

The meta-analysis by Meng et al. (227) included 23 publications (33 studies), published between 1986-2013, analyzing associations of neural tube effects in utero with maternal active or passive smoking during or before pregnancy. Overall, maternal passive smoking significantly increased the risk of having infants with neural tube defects. No association was found for maternal active smoking during pregnancy. The heterogeneity between the studies was moderate. A previous systematic review on neural tube defects by Wang et al. (201) was not considered in the umbrella review due to the lower number of studies evaluated. The level of **evidence was not assessed** by the study authors, however, the umbrella review by Rojas-Rueda (38) rated the strength of **evidence as low**.

Yu et al. (226) addressed the question of whether maternal smoking during pregnancy carries an increased risk of cryptorchidism in male infants. The meta-analysis included 20 studies, published between 1984-2012. Overall, the analysis indicated **sufficient evidence** for a positive association between prenatal maternal smoking and the risk of cryptorchidism in male infants. Analyses on a dose-response relationship remained inconsistent. However, it must be noted that this meta-analysis was based on pooled crude effect measures. Yet, the Surgeon General's Report (220) also rated the association with maternal prenatal smoking as **suggestive evidence.**

All meta-analysis reported that prenatal SHS exposure was linked to significantly increased risks of all described congenital malformations or defects. However, there were differences, if the mother smoked during pregnancy or was exposed to passive smoke herself.

### Preterm birth

Preterm birth associated with prenatal maternal SHS exposure was studied by one meta-analysis (233). The analysis was of good quality, using three different literature databases and the Newcastle-Ottawa Scale as well as the "agency for healthcare research and quality" criteria to assess study quality. Cui et al. (233) included 24 studies published between 1986-2014. The analysis revealed that maternal SHS exposure during pregnancy (at any place or at home) significantly increased the risk of preterm birth. However, the level of **evidence was not assessed** by the study authors, yet the Surgeon General's Report (220) assessed the association with maternal prenatal smoking as **sufficient evidence**.

### Fetal measurements

The meta-analysis by Abraham et al. (229) investigated the effect of maternal smoking during pregnancy on fetal measurements. The analysis was of good quality, using three different literature databases and the "effective public health practice project" tool to assess study quality. The authors examined fetal measurements at three different times during pregnancy (first, second and third trimester), including crown rump length, biparietal diameter, head circumference, abdominal circumference, mean abdominal diameter, femur length and estimated fetal weight. In total, 18 studies were reviewed and eight included in the meta-analysis, which were published between 1987-2013. Overall, maternal smoking during pregnancy was associated with a decrease in fetal size and growth after the first trimester, particularly reduced head and femur length. Smoking cessation or reduction during pregnancy might mitigate negative consequences. However, the level of **evidence was not assessed** by the study authors, yet the Surgeon General's Report (220) rated the association with fetal growth restrictions as **sufficient evidence**.

### Mortality outcomes

Three meta-analyses were included, assessing the relationship between prenatal smoke exposure and miscarriage, perinatal death or SIDS. The reviews were of limited quality. Pineles et al. (230) and Pineles et al. (231) both used only one literature database, whereas Zhang et al. (232) used at least two. To assess study quality Pineles et al. (230) and Pineles et al. (231) used selected indicators to address information bias, confounding, selection bias, and violation of statistical assumptions. Zhang et al. (232) based the study evaluation on six criteria developed by the American Academy of Pediatrics Task Force on Positioning and SIDS.

The risk of miscarriage (also referred to as spontaneous abortion) associated with prenatal maternal (active and passive) smoking as well as any maternal active smoking in life was explored in the meta-analysis by Pineles et al. (230). The authors examined 112 studies and included 98 in the meta-analysis, which were published between 1963-2010. Overall, maternal active smoking during pregnancy or in general significantly increased the risk of miscarriage. Analyses on a dose-response relationship also revealed a significantly increased risk of miscarriage with increasing maternal cigarette consumption. In contrast, prenatal maternal SHS exposure did not show a significant effect. The heterogeneity between the studies was moderate. Overall, the authors state that the study results further **strengthen the evidence** for an association for this risk-outcome pair. The Surgeon General's Report (220) rated the **evidence as suggestive** for maternal active smoking during pregnancy. A previous meta-analysis on miscarriage by Leonardi-Bee et al. (200) was not considered in the umbrella review due to the lower number of studies evaluated.

Pineles et al. (231) assessed the role of prenatal maternal (active and passive) smoking in association with perinatal death and its two components stillbirth and neonatal death. In total, 200 studies were reviewed and 142 included in the meta-analysis, which were published between 1959-2011. Overall, perinatal death, stillbirth and neonatal death were all significantly associated with any active maternal smoking. A dose-response-relationship was confirmed for an increased risk of all three mortality outcomes with increased maternal smoking rates. In addition, maternal SHS exposure during pregnancy also significantly increased the risk of stillbirth and perinatal death. Neonatal deaths were examined by one study only. The

heterogeneity between the studies was mostly moderate and publication bias was detectable, though not significant. As for the risk of miscarriage, the authors state that the study results further **strengthen the previous evidence** for an association for this risk-outcome pair. The Surgeon General's Report (220)assessed the **evidence as sufficient** for maternal prenatal smoking. A previous meta-analysis on perinatal death, stillbirth and neonatal death by Leonardi-Bee et al. (200) was not considered in the umbrella review due to the lower number of studies evaluated.

Zhang et al. (232) conducted a meta-analysis on prenatal and postnatal maternal smoking in relation to SIDS in infants younger than one year. In total, 35 studies were included, published between 1992-2011. The results indicated that both prenatal and postnatal maternal smoking were significantly associated with increased SIDS risk. Though, prenatal smoking was a bigger contributor to the development of SIDS than postnatal smoking. In addition, a dose-response relationship was confirmed, comparing tobacco consumptions above and below ten cigarettes per day. Overall, heterogeneity between studies was moderate to substantial. The level of **evidence was not assessed** by the study authors. Yet, the Surgeon General's Report (220) rated the association with SHS exposure as **sufficient evidence.** A previous meta-analysis on SIDS by Röösli et al. (202) was not considered in the umbrella review due to the lower number of studies evaluated.

All meta-analysis reported that maternal smoking during and after pregnancy was linked to significantly increased risks of all three described mortality outcomes. However, there were differences, if the mother was exposed to passive smoke herself.

#### Malignant neoplasms

One meta-analysis and one systematic review (including meta-analyses when possible) assessed the role of SHS exposure in leukemia and brain tumors, respectively. Both publications reported results on prenatal and postnatal exposure (Table 82).

**Table 82: Summary table on malignant neoplasms attributed to secondhand smoke**

| Outcome | First author (year) | Population /age group | Exposure time not differentiated | Exposure prenatal | Exposure postnatal | Main results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|---|---|---|
| Brain tumors | Zumel-Marne (2019) | <25 years | Overall | Mother (active and passive smoking) | Parents | Maternal smoking during pregnancy (actively and passively) significantly increased the risk of brain tumors. Effects of postnatal exposure on children were consistent. | NR | (206) |
| Leukemia | Chunxia (2019) | <15 years | Overall | Mother (active smoking), father (active smoking) | Mother, father | Maternal smoking before, during, or after pregnancy was not significantly associated with childhood ALL or AML. Paternal smoking during pregnancy significantly increased the risk for childhood ALL but not for AML. The higher the consumption of paternal smoking | Productive evidence (paternal smoking) | (234) |

| Outcome | First author (year) | Population /age group | Exposure time not differentiated | Exposure prenatal | Exposure postnatal | Main results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|---|---|---|
| | | | | | | during pregnancy was, the higher the risk of childhood ALL or AML. | | |

Notes: NR = not reported

The two reviews were of mixed quality. The risk of bias was only assessed by Zumel-Marne et al. (206) using the "strengthening the reporting of observational studies in epidemiology" statement. However, both publications were based on at least three literature databases.

The systematic review by Zumel-Marne et al. (206) evaluated different risk factors associated with brain tumors in young people under 25 years of age. The age group considered was expanded in this case, as only three of the 24 included studies on SHS exposure published between 1979-2016 investigated people older than 20 years. Meta-analyses were conducted when possible. Meta-analytical results revealed that maternal active and passive smoking during pregnancy significantly increased the risk for brain tumors in children and young adults. The heterogeneity of the studies was low to moderate. One of three studies reported significant associations with postnatal parental exposure. Overall, the authors suspect a possible link between passive smoking and brain tumors. However, the level of **evidence was not assessed** by the study authors.

Acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) associated with prenatal (mother, father) and postnatal (mother, father) SHS exposure was studied by Chunxia et al. (234). The meta-analysis included 19 studies on children younger than 15 years, published between 1974-2018. No statistical association was found between maternal smoking during or after pregnancy and ALL or AML. However, paternal smoking during pregnancy as well as paternal overall SHS exposure increased the risk for ALL, but not for AML. The heterogeneity of the studies was moderate. Overall, the analysis **adds further evidence** for a link between childhood AAL and paternal smoking. Furthermore, the umbrella review by Rojas-Rueda (38) rated the strength of **evidence for ALL and AML as moderate**.

#### Others

In addition to the diseases described above, other diseases identified in the umbrella review are suspected to be associated with SHS exposure in children. Outcomes related to neurologic effects, endocrine or metabolic effects as well as not further categorized diseases are listed in Table 83, Table 84 and Table 85, together with selected characteristics of the respective systematic reviews or meta-analyses.

### Table 83: Summary table on all neurologic effects attributed to secondhand smoke

| Outcome | First author (year) | Population/ age group | Exposure prenatal | Exposure postnatal | Main results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|---|---|
| ADHD | Dong (2018) | Offspring | Mother (active and passive smoking) | | Maternal smoking during pregnancy or smoking cessation during the first trimester was significantly associated with childhood ADHD. Inconsistent results were reported on the risk of maternal passive smoke exposure during pregnancy. | NR | (235) |
| ADHD | Huang (2021) | <18 years | | Household | Significantly increased ADHD risk with postnatal SHS exposure | NR | (236) |
| Autism spectrum disorder | Jung (2017) | Offspring | Mother (active smoking) | | Non-significantly increased ASD risk with maternal smoking during pregnancy with high heterogeneity. However, subgroup analyses suggest that a more nuanced interpretation is warranted. | NR | (237) |
| Cognitive impairment | Chen (2013) | ≤18 years | Mother (passive smoking) | Mother, father, household, other persons in household | Prenatal SHS exposure showed strong associations with reduced neurodevelopment especially in young children. Postnatal SHS exposure is associated with poorer cognitive function later in childhood (poor academic achievement and neurocognitive performance, neurodevelopmental delay). | NR | (238) |
| Obstructive sleep apnoe | Chang (2022) | <18 years | | Mother, father, household | Significantly increased obstructive sleep apnoe risk with postnatal SHS exposure. Higher odds ratios were shown by maternal smoking than by paternal smoking. | NR | (239) |

Notes: NR = not reported

**Table 84: Summary table on all endocrine and metabolic effects attributed to secondhand smoke**

| Outcome | First author (year) | Population/ age group | Exposure prenatal | Exposure postnatal | Main results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|---|---|
| Metabolic syndrome | Chen (2019) | 1-19 years | | household, other places | The association of metabolic syndrome with SHS varies with age. When exposed to SHS, children/adolescents may be more susceptible to lipid metabolic disorder (compared to adults). Regarding abdominal obesity, SHS exposure had a positive impact on body mass index and was positively associated with waist circumference in children/adolescents. | NR | (124) |
| BMI, overweight | Magalhães (2019) | >2 to 19 years | Mother (active smoking) | | Maternal smoking during pregnancy significantly increased the odds of children's overweight and body mass index mean difference. | Low (BMI) to moderate (overweight) | (240) |
| Overweight/ obesity | Qureshi (2018) | 0-18 years | Mother (passive smoking) | | Significantly increased risk of obesity for maternal SHS exposure during pregnancy, whereas overweight was not significantly associated with an increased risk. Due to high heterogeneity between studies, the results need to be interpreted with caution. | Equivocal | (241) |
| Puberty timing | Chen (2018) | In utero up to adulthood | Mother (active smoking) | Person not specified | Not entirely consistent results for SHS exposure on age of menarche. Maternal smoking during pregnancy possibly decreases the age of menarche in girls. Prenatal passive smoke exposure was not significantly associated with an increased risk. However, overall SHS exposure significantly decreased the age of menarche in girls. | Not strong, suggestive | (242) |

Notes: NR = not reported

**Table 85: Summary table on other effects attributed to secondhand smoke**

| Outcome | First author (year) | Population/ age group | Exposure time not differentiated | Exposure prenatal | Exposure postnatal | Main results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|---|---|---|
| Child growth | Nadhiroh (2020) | <8 years | | Person not specified | Person not specified | SHS exposure may be associated with adverse growth outcomes. Pre- or postnatal exposure was inversely associated with weight, height and elevated BMI of children. Furthermore, prenatal SHS exposure was associated with a lower head circumference. | NR | (243) |
| Caries | González-Valero (2018) | <20 years | Overall | Person not specified | Person not specified | A significant, though moderate association was found between any type of SHS exposure and caries. | NR | (204) |
| Periodontal status | Oliveira (2022) | <16 years | Overall | | | SHS exposure is possibly associated with poorer periodontal status due to higher levels of gingivitis. | Very low confidence | (244) |
| Inflammatory bowel disease | Agrawal (2021) | Early life (in utero until 5 years of age) | | Mother (active smoking) | | Maternal smoking during pregnancy significantly increased the risk of developing IBD, though significant heterogeneity was identified. Additionally, IBD subtype analyses were not significant. | Not consistent | (245) |
| Legg-Calvè-Perthes disease | Gao (2020) | Children | | Mother (active smoking) | Mother, father, household | Significantly increased risk of Legg-Calvè-Perthes disease for any type of SHS exposure (prenatal and postnatal), though not significant for the European population. Additionally, prenatal and postnatal maternal smoking may show a dose-response relationship. | NR | (246) |
| Surgical outcomes | Chiswell (2017) | ≤18 years | | | Person not specified | SHS exposure significantly increased the risk of respiratory adverse events during anesthesia in surgery and may also negatively impact surgical outcomes in children. | Sufficient evidence (anesthetic complications) | (247) |
| Blood pressure | Aryanpur (2019) | <18 years | Overall | Person not specified | Household | Pre- and postnatal SHS exposure was not significantly associated with developing hypertension. However, SHS was significantly associated with higher level of systolic blood pressure. | NR | (248) |

| Outcome | First author (year) | Population/ age group | Exposure time not differentiated | Exposure prenatal | Exposure postnatal | Main results | Evidence level by reviews | Reference |
|---|---|---|---|---|---|---|---|---|
| Carotid intima-media thickness | Shu (2022) | <18 (5-16) years | Overall | Mother (active smoking) | Mother, household | Most of the included studies found a significant association between overall SHS exposure and carotid intima-media thickness. However, results on maternal exposure (prenatal and postnatal) were inconsistent. A dose-response relationship was reported when using cotinine as SHS biomarker. | NR | (249) |
| Vascular effects | Georgiopoulos (2021) | ≤21 years | Overall | | | SHS exposure was reliably associated with worse endothelial function. | NR | (205) |

Notes: NR = not reported

#### Health effects on adults associated with SHS exposure during pregnancy or childhood

Within the umbrella review, six systematic reviews or meta-analyses were excluded in the full text screening process that investigated SHS exposure during pregnancy or childhood related to health effects in later adulthood. These looked at five other outcomes: Two reviews reported on COPD (250,251), one on endometriosis (252), one on Parkinson disease (253), one on urothelial bladder cancer (254) and one on schizophrenia (255). Since the adult population was not the target group in this review, this list of associated diseases is not comprehensive.

***Discussion***

Long-term and short-term SHS exposure has been shown to cause a variety of severe health effects to the unborn child, infants, children and adolescents. We identified 44 systematic reviews or meta-analysis investigating 44 specific health consequences associated with pre- or postnatal SHS exposure at home. Most effects were related to respiratory effects or birth outcomes.

Table 86 provides an overview of all health outcomes identified in our umbrella review that are associated with SHS exposure and for which strong evidence was reported. The evidence levels were assessed by the respective study authors of the identified systematic reviews or meta-analyses (where available). Also listed are the ratings of the Surgeon General's Report (220) and the umbrella review by Rojas-Rueda (38) for these outcomes. The interpretation of the evidence levels should be done with caution, as the evidence base differs between the respective sources. This holds both for the number of studies considered in the assessments and also for the timeliness.

**Table 86: Identified health effects attributed to secondhand smoke exposure in children or adolescents with strong evidence levels as reported by respective study authors or other selected reports/reviews**

| Health outcome | | Evidence level assessed by: | | |
|---|---|---|---|---|
| | | **Surgeon General's Report 2014** (220) | **Rojas-Rueda** (38) | **Respective study authors (reference)** |
| Respiratory effects | Asthma, wheeze (onset) | Suggestive (asthma), sufficient (wheeze) | Low | Considerable (211) |
| | Asthma attacks/exacerbation | NR | NR | Highly confident (210) |
| | LRI | Sufficient | NR | NR (214,215) |
| | Otitis media (also called middle ear disease/infection) | Sufficient | Low (otitis media) | NR (216) |
| Birth outcomes and developmental effects | SIDS | Sufficient | NR | NR (232) |
| | Preterm birth | Sufficient | NR | NR (233) |
| | Cryptorchidism | Suggestive | NR | Sufficient (226) |
| | Oral clefts | Sufficient | NR | NR (228) |
| | Fetal measurements | Sufficient (fetal growth restriction) | NR | NR (229) |
| | Perinatal death | Sufficient | NR | Strengthened (231) |
| Others | Surgical outcomes | NR | NR | Sufficient (247) |

Notes: NR = not reported.

The vast majority of all systematic reviews or meta-analyses reported at least one evaluation that showed an increased risk for the respective disease associated with SHS exposure. In addition to the general SHS exposure from the household, the focus was often on the effect of the exposure resulting from actively or

passively smoking mothers. Exposure-response relationships were rarely reported in the reviews. This might be because only few studies explored such relationships and thus pooling was not possible. However, the identified studies on SHS exposure related health outcomes showed a high heterogeneity regarding sample size, age ranges and methods used to assess the exposure. For most outcomes only one publication was identified, sometimes including a small number of studies. Besides, the study base for describing or deriving effect measures for different exposure time windows, outcome subtypes or other sub-analyses (e.g. differentiation by study quality, design or region) was even smaller and weakened the statistical associations. The results derived from these reviews on possible links to SHS exposure can therefore only be interpreted as indicative, but do not yet allow an overall assessment of the evidence. In contrast, asthma development or asthma exacerbation were outcomes most frequently studied in relation to SHS exposure in children. Previous analyses showed similar significant associations as identified in our umbrella review. However, the heterogeneity between the individual studies included in the meta-analyses was very high. Differences were often mainly due to different definitions of outcomes or exposures. Despite good data availability, these limitations have a strong impact on the overall evidence assessment for asthma.

Another limitation that applied to almost all reviews was the way SHS exposure was assessed. For feasibility reasons, self-reported data are often used in epidemiological studies to determine SHS exposure, because this method is applicable at comparable low cost. The assessment can however be subject to social-desirability bias, as the participants may not truthfully report or misestimate their smoking behaviour or SHS exposures (256). Consequently, actual exposure may be underestimated, and health associations statistically attenuated. For a better exposure assessment, (additional) biomarker measurements, such as cotinine in urine, are recommended. Apart from that, the exposure data often do not allow differentiation according to whether children lived with people who smoke inside or outside the home. Secondly, it is extremely difficult to disentangle prenatal from postnatal effects since both exposure times are highly correlated and subject to misclassification.

Moreover, the validity of the review results was also hampered by the fact that the identified systematic reviews or meta-analyses were often predominantly based on cross-sectional studies or case-control studies. Though, a causal relationship between SHS exposure and investigated diseases cannot be concluded from such results. This was also one of the reasons that made it difficult to assess the evidence for different risk-outcome pairs.

Our umbrella review also had some methodological limitations. With regard to the literature searched, we exclusively included systematic reviews or meta-analyses and no primary studies. This poses the risk that most recent studies on health effects related to SHS exposure in children and adolescents have not yet been considered. In addition, the selection of publications was based on extended inclusion criteria, including the timeliness or the comprehensiveness of the respective reviews. Furthermore, a graded evidence assessment was not performed on the basis of the identified literature. Further limitations were that only publications in English language and no narrative reviews, grey literature or conference papers were considered.

### *Conclusions*

Our umbrella review showed that SHS exposure is associated with a huge variety of negative health effects for unborn children, infants, children and adolescents. They are particularly affected by respiratory effects and outcomes related to SHS exposures during pregnancy. Although the evidence is not yet sufficient for some of the listed diseases, the results clearly underline the relevance of the risk factor for population health. Children and adolescents are a vulnerable group in our society. This is especially true since they have no possibility to reduce their SHS exposure at home and are dependent e.g. on their parent's behaviour. The implementation of national smoke-free legislation or other tobacco prevention policies has led to a significant reduction of SHS exposure in public spaces of many European countries. The growing awareness of the problem in the private environment eventually also have improved the exposure situation for children and adolescents at home. However, strong efforts are still needed to further reduce SHS exposure for children to protect them from associated health risks. In this regard, parents and other family members should be aware and encouraged to establish smoke-free environments for their children.

This especially applies to the time during pregnancy but also later in all critical developmental time windows. Eventually, all diseases or deaths attributable to SHS exposure are preventable.

### 3.2.2 Formaldehyde

#### *Exposure risk characterization and overview of current exposure of and impacts on children and adolescents in Europe*

Formaldehyde has been produced on a large scale for more than 100 years. It is not only used as a binding agent in chipboard, but also, for example, as a preservative in paints, varnishes and cosmetics, as an easy-to-clean additive in textiles, as a disinfectant and in the production of synthetic resin. Besides the technically produced formaldehyde, this substance is also found in large quantities as a product of incomplete combustion processes, e.g. in motor vehicle exhaust fumes and cigarette smoke. Due to its widespread usage, it is almost impossible to avoid this chemical nowadays.

The main effect of inhaled formaldehyde is considered to be the irritation of the upper respiratory tract. Chronic exposure to very high concentrations of formaldehyde may cause cytotoxic and carcinogenic effects in this tissue. Several documentations that evaluated the toxicological effects of exposure to formaldehyde by inhalation are published. These include reviews by Nielsen and Wolkoff (257) and Nielsen et al. (258) on the WHO indoor air guideline value (49), the German Federal Institute for Risk Assessment (BfR in German) paper (259) or the European Chemicals Agency (ECHA) dossier (260) and related comments by the Risk Assessment Committee (RAC) (261).

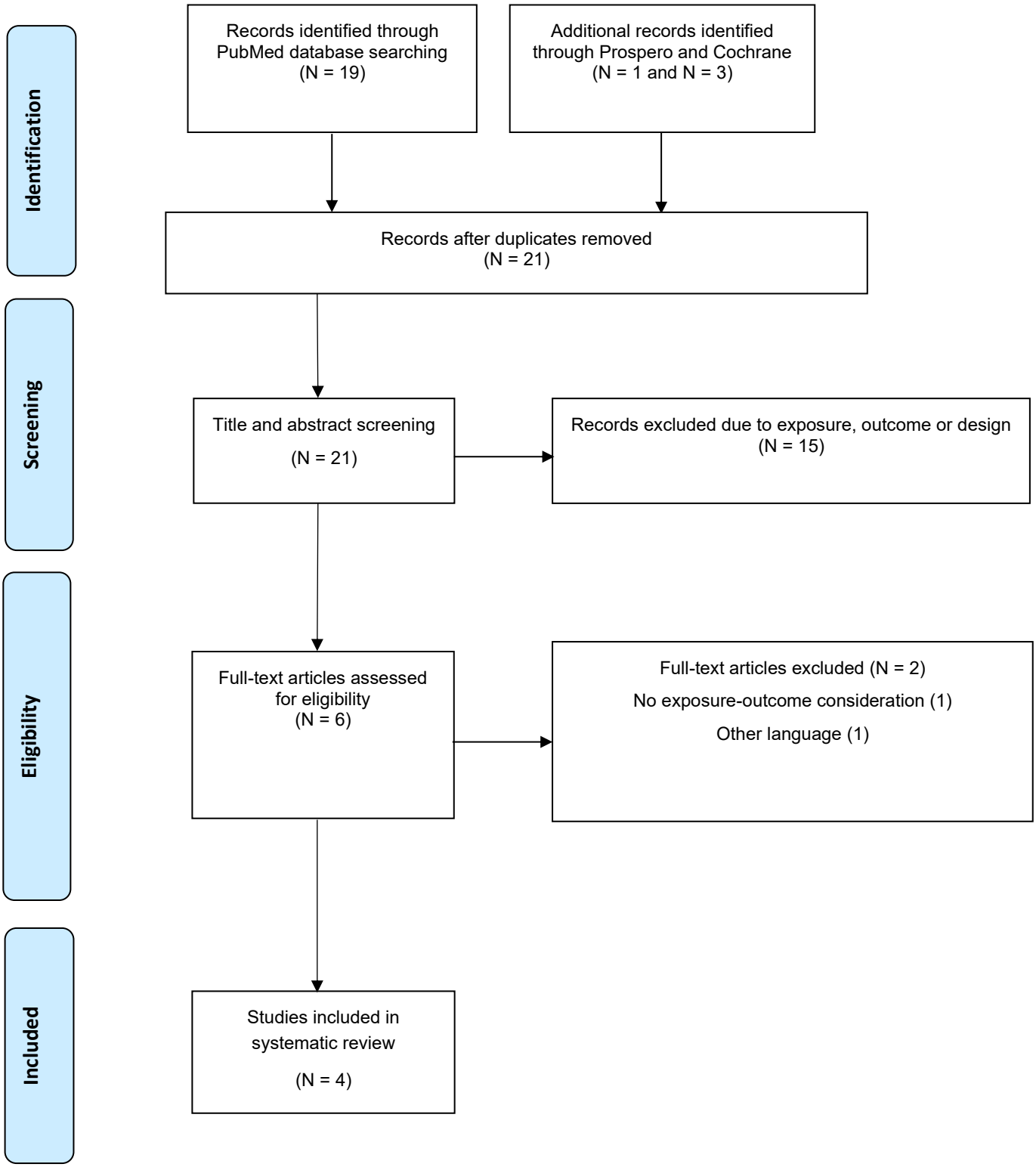
Some published studied reported enhanced asthmatic complaints among children at increased indoor air concentrations of formaldehyde. However, whether inhaled formaldehyde can also reach deeper parts of the respiratory tract and trigger or aggravate asthma, especially in children, is a controversial issue.

Extensive data on indoor air formaldehyde levels can be found in the literature (262). Comparisons are often challenging due to different aims, quality and designs of the measurement campaigns. Formaldehyde concentrations were measured in children's rooms in the German environmental surveys (GerES) IV (2004-2007) (263) and GerES V (2014-2017) (264). Median concentrations of 23.5 µg/m³ (GerES IV) and 24.9 µg/m³ (GerES V) show that children's exposure to formaldehyde remained at a very similar level in recent years although other aldehydes show a decreasing trend during the last years (265).

#### *Study search and selection*

The literature search according to the methodology described in Section 2.2 initially identified 21 records after removal of duplicates (Figure 10). 15 records were excluded after title and abstract screening due to unsuitable and/or missing exposure pathways, health outcome or study design. Full-text assessment of the articles led to exclusion of one record (266) because there was no exposure-outcome consideration as requested by our inclusion/exclusion criteria. One record was not considered for the umbrella review as it is written in German (267). However, the information in this paper was used as it is highly relevant for the current topic. Finally, four studies met the selection criteria and were included in the umbrella review (268–271).

**Figure 10: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram for the search of selected health effects on children due to formaldehyde. Search date 1.06.2022**




***Study characteristics and quality assessment***

The following characteristics were extracted into a table (see Appendix C) from the four reviews included in this umbrella review: first author, year of publication, reference, reported health outcome, health outcome measure, pollutant(s), setting, exposure ranges, meta-analysis, number of primary studies included, search period, databases searched, publication year range, world regions included, number of people / cases included in review, a risk of bias assessment tool used, assessment of presence and likely

impact of publication bias, main results from abstract and / or text, effects [+, (+), 0, (-),-], increment of exposure, metric [HR, OR, RR], estimate, 95%-CI, meta-analysis model, heterogeneity measure (value).

All four included records in the umbrella review provided detailed information about the methodology for conducting the review work, e.g. inclusion and exclusion criteria of studies, quality assessment of the literature, risk of bias assessment or statistical analysis. Therefore, the four reviews are considered to be of moderate to high quality. All the original studies comprised in the review articles were not checked in detail as it was not within the scope of this umbrella review. However, it has to be mentioned that several studies included in the reviews have been critically discussed in other publications. This issue will be considered in the discussion.

***Health outcomes and evidence***

All selected review articles covered the question, whether there is an association between formaldehyde exposure indoors and health outcomes such as asthma, asthma diagnosis or exacerbation of asthma symptoms in children or in children and adults. Hence, only this health outcome is examined in this report. The indoor settings considered in the children's studies were homes and schools.

Lam et al. (268) conducted a systematic review and meta-analysis to determine the association between formaldehyde exposure and asthma diagnosis or exacerbation of symptoms in children and adults. Furthermore, a benefit-cost analysis was performed to assess the economic benefit of formaldehyde regulation to decrease indoor exposure resulting in fewer asthma cases annually. The authors concluded that there is 'sufficient evidence' for associations between formaldehyde exposure and asthma diagnosis and symptoms in children and adults. An OR of 1.2 (95% CI, 1.02-1.41) for increased asthma diagnosis in children and 1.08 (95% CI, 0.92-1.28) for exacerbation of asthma were calculated per 10 µg/m³ unit increase in formaldehyde exposure. Decrease of formaldehyde exposure due to regulation (implementing emission limits for composite wood products) may lead to 2,805 fewer asthma cases in the U.S. and thus save costs of 210 million US dollars.

Yu et al. (269) meta-analysed the results of 13 studies to examine the association between indoor formaldehyde exposure and asthma in children and adults. The authors found that an increase of formaldehyde exposure by 10 µg/m³ was significantly associated with a 10 % increase in the risk of asthma in children.

Yao et al. (270) reported on a meta-analysis of six articles published between 1995 and 2014 to assess the relationship between formaldehyde exposure and asthma in children. The authors calculated a weighted mean difference (WMD) in concentration of formaldehyde of 0.021 (95% CI (confidence interval): 0.009-0.033) between control group and children with asthma. This value implies that the average formaldehyde concentration in the environment of the case group was higher than the average formaldehyde level in the environment of the control group. The authors concluded that higher levels of formaldehyde indoors may lead to higher risk of asthma development in children.

McGwin et al. (271) published a systematic review and meta-analyses aiming to identify the association between formaldehyde exposure and asthma in children. OR and CI were extracted from each study. The authors calculated an OR of 1.03 (95% CI, 1.02-1.04) using a fixed-effects model and an OR of 1.17 (95% CI, 1.01-1.36) both reflecting a 10 µg/m³ unit increase in formaldehyde exposure. The authors concluded that results of the literature search indicate a positive association between formaldehyde exposure and asthma in children.

***Discussion***

The authors of the four review articles concluded that in general there is a positive association between indoor formaldehyde exposure and childhood asthma or even an increase of asthma risk in children with an increase of formaldehyde exposure by 10 µg/m³. These conclusions need to be critically discussed by examining the original studies in more detail. This has been done in various publications (257,258,267,272).

Published original studies on this topic that are also included in the four review articles show contradictory results. For example, Dannemiller et al. (273), Garrett et al. (274), Rumchev et al. (275), Venn et al. (276), Zhai et al. (277) reported on the increased prevalence or intensification of asthmatic complaints among

children in relation with formaldehyde exposure. Venn et al. (276) analysed concentrations of formaldehyde, nitrogen dioxide, total volatile organic compounds and levels of damp and environmental tobacco smoke in 193 children with persistent wheezing and 223 controls in England. No increased risk of wheezing in relation to the formaldehyde concentration was determined in the children's bedroom. Only for the damp factor a correlation with an increase of wheezing was described. However, formaldehyde concentration was associated with the number of nocturnal symptoms among the children with persistent wheezing. The conclusion of the authors was that formaldehyde is more likely to increase the severity of symptoms. In a study published in 2002 Rumchev et al. reported on the increase of asthmatic symptoms by about 39% associated with an increase of formaldehyde levels from 10 µg/m³ to about 60 µg/m³ (275). In a publication from 2004 (278), Rumchev et al. analysed correlations between indoor exposure to volatile organic compounds and asthma in young children aged between 6 months and 3 years, the same study population used in the study published in 2002. The authors stated that the risk of having asthma in children may increase by nearly two and three times for every 10 unit increase in the indoor levels of toluene and benzene. Since benzene and formaldehyde can be found indoors as products of combustions processes the conclusions regarding associations of asthma and formaldehyde need to be checked more in detail.

Some publications contradict such associations (257,258,272,279) and pointed to the limitations of some of the above-mentioned studies. According to Heinrich (279), the incidence of asthmatic complaints is considered to be much more related to exposure to tobacco smoke, indoor air humidity or close proximity of the home to road traffic.

The German Committee on Indoor Air Guide Values (AIR) published an article in 2016 in German, solely dedicated to the question whether indoor formaldehyde exposure is associated with asthma diagnosis or exacerbation of asthma symptoms in children (267). The authors reviewed the relevant literature and included summaries of the original studies sorted by study design. They also examined two of the meta-analyses included in this umbrella review, the ones by McGwin et al. (271) and Yao et al. (270). The review by Yao et al. could not be checked in detail as the full text of some Chinese original studies could not be retrieved. Furthermore, one paper reported on adults and not children. Many of the original studies included in the reviews by Yu et al. (269) and Lam et al. (268) were discussed in the paper of the AIR committee.

McGwin et al. (271) found a positive association between formaldehyde exposure and asthma in children. Nevertheless, this statement does not confirm a causal relationship all the more since the authors indicate tobacco smoke and humidity as confounding factors. Burning processes lead to the emissions of other compounds that are structurally analogous to formaldehyde (e.g., unsaturated aldehydes). This means that additive effects play an important role and thus the sum of volatile compounds should be always measured in such studies. Only very few studies provide such data. McGwin et al. suggested that more studies are needed for a better assessment.

The German AIR Committee concluded that there is no reliable evidence or dose-response relationship for triggering new asthma cases or exacerbations of asthma in children by formaldehyde in indoor air (267). This opinion is supported by reports from other international committees like the WHO (34) or the Agency for Toxic Substances and Disease Registry (ATSDR) (280) and by data from animal studies.

Many studies included in the review articles indicated high interrelationship of multiple individual factors. Higher levels of formaldehyde indoors may also indicate the presence of other substances that need to be measured in these studies. Low air change rates and higher humidity can lead to increased exposure to mould. Respiratory infections in such rooms that are usually ventilated insufficiently may be accompanied by asthmatic symptoms, but these cannot be considered as evidence of asthma in the proper sense. The implications of individual epidemiological studies are often further limited by small sample sizes. Generally, it is difficult to diagnose asthma in children, many of the studies included in the reviews relied only on parent questionnaire for this. Furthermore, in some studies definition of asthma is inconsistent or missing.

With respect to environmental burden of disease assessments for formaldehyde, Rojas-Rueda and colleagues (7) estimated the burden attributable to formaldehyde exposure in European children and adolescents aged up to 3 years. The burden was mainly associated with asthma and was very low, only accounting for 33 DALYs in the under 3 year of age population in Europe (7).

In conclusion, it seems to be **problematic to assume or deny a causal relationship** between indoor formaldehyde exposure and asthma in children. Prospective studies that address the complex exposure situation of children are necessary for a comprehensive evaluation of this issue. However, it is undoubtedly that exposure to indoor pollutants should be reduced to levels as low as possible so that children live and grow up in a healthy indoor environment.

### *3.2.3 Dampness and mould*

#### *Exposure risk characterization and overview of current exposure of and impacts on children and adolescents in Europe*

Every sixth household in European countries is impacted by dampness (281). Humidity as a climate factor is increasingly considered as a potential health risk, however it is unclear to what extent dampness/humidity itself is a health risk in indoor environments. In studies on mould exposures, humidity is commonly used as a parameter for mould growth, since it is easier to measure than microbial parameters and is strongly related to mould infestation. Mould is commonly caused by increased humidity/dampness through, water damages, building shortcomings or elevated relative humidity due to room use, and/or insufficient ventilation. The exposures in mouldy indoor environments are complex and diverse. A number of micro-organisms, such as mould fungi, yeasts, bacteria - especially actinobacteria - and organisms that can use mould as a food source, such as mites, are related to mould infestation. Furthermore, microbial metabolites and other microbial substances such as toxins, endotoxins, allergens, β-glucans, microbial volatile organic compounds (MVOC) and microbial fragments such as conidia and fragments of mycelia released to and detected in indoor air and dust in households with mould infestation.

Mould effects can be related to adverse health disorders. Sufficient evidence for a causal relationship between moisture/mould damage and health effects has so far been established for allergic bronchopulmonary aspergillosis (ABPA) and mould-induced mycoses, allergic respiratory disease, asthma (manifestation, progression and exacerbation), allergic rhinitis, hypersensitivity pneumonitis (extrinsic allergic alveolitis), and increased likelihood of respiratory infections/bronchitis (282). Further mould related health disorders, that are occasionally reported but with insufficient evidence, include atopic eczema/neurodermitis (manifestation, progression and exacerbation), cough, Mucous Membrane Irritation Syndrome (MMI), wheeze and mood disorder.

According to current knowledge, irritations of the eyes and of the mucous membranes of the respiratory tract as well as allergic reactions and diseases are the most prevalent health outcomes of the exposure with mould (282).

Children are considered to react more sensitively to mould and dampness due to several physiological properties (less developed immune system, developing lung system, higher respiration rate). Young children are in closer contact and physically closer to the floor surface (or ground) because of their height. Therefore, they are more likely to be exposed to sedimented dust (that frequently contains mould particles) on the floor, on carpets and to near-floor-mould-damages. Toddlers also have more physical (skin and hand-to-mouth) contact to floors and dust on floors than adults. These properties might lead to a higher exposure of children to mould compared to adults.

In the adolescence, the exposure routes become increasingly similar to those of adults, with inhalation considered to be the main route of exposure. However, there are also fewer studies that cover the age group < 10 years and adolescents.

In the United States, the annual costs of mould/dampness in homes for the society are calculated to be 3.7 (2.3 – 4.7) billion US-dollar for allergic rhinitis, 1.9 (1.1 – 2.3) billion US-dollar for acute bronchitis, 15.1 (9.4 – 20.6) billion US-dollar for asthma and 1.7 (0.4-4.5) billion US-dollar for asthma-death rate (283).

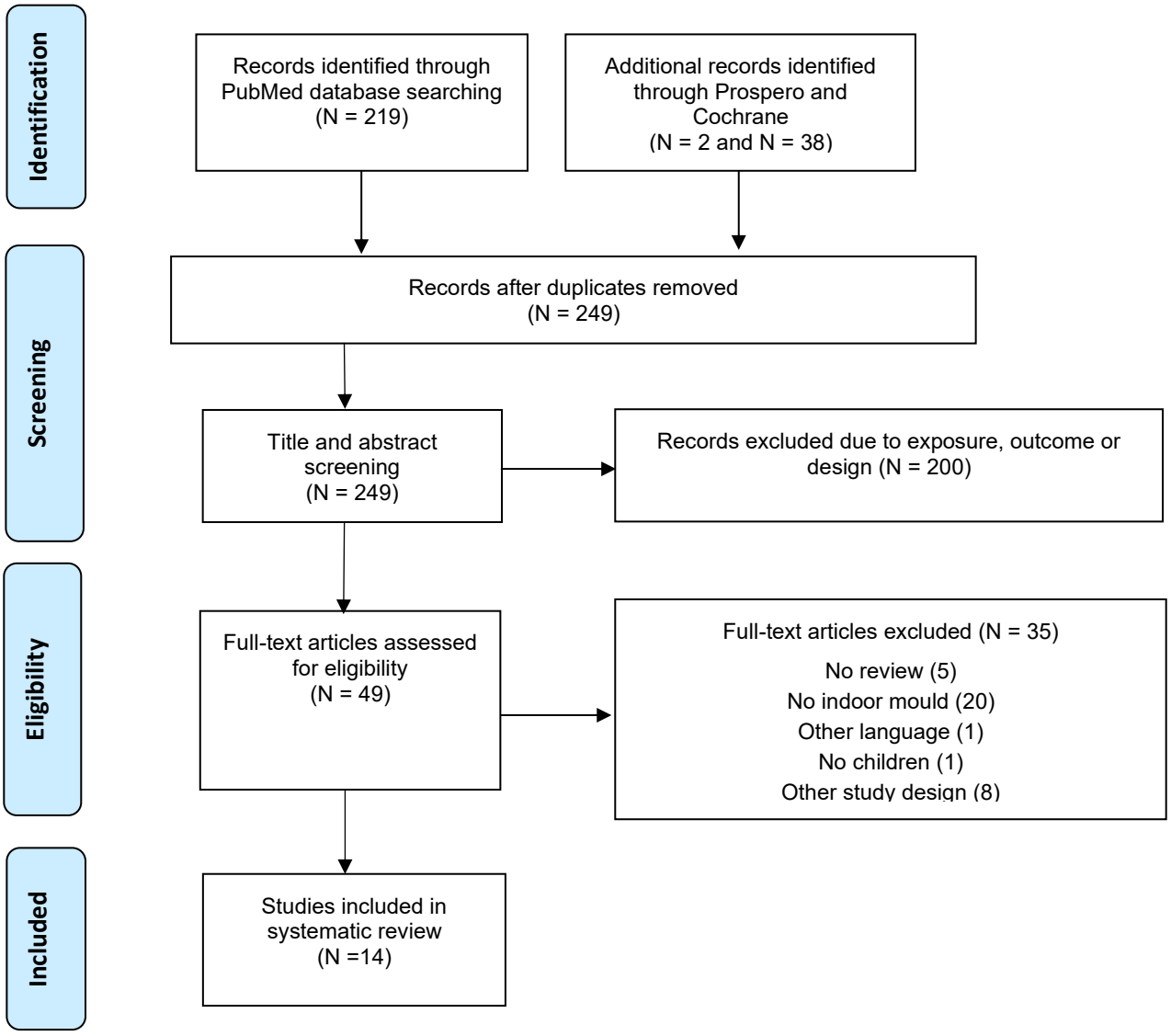
Although we performed an extensive literature research, we were not able to find existing equivalent data for Europe.

***Study search and selection***

The literature search for mould was conducted in the three databases on 31 May 2022 and in accordance with the methodology described in Section 2.2. The search in PubMed yielded 219 hits, Cochrane 38 hits and PROSPERO 96 hits. The hits in PROSPERO were screened individually, because the database includes study protocols. The related published articles are linked. Thus, first the study protocol was screened and once it was selected as applicable based on the inclusion and exclusion criteria the article was included in the EndNote database.

The EndNote database for the screening step included 219 hits from PubMed and 38 hits from Cochrane. Out of the 257 articles 15 were duplicates and two articles from PROSPERO were already found through the PubMed search. Consequently, a total of 249 articles was eligible for title and abstract screening. Out of these 29 were classified as “need to discuss”. Therefore, a mould specialist and a medical specialist for hygiene and environmental medicine were consulted and the articles were conclusively classified as relevant or not, leading to a total of 200 articles excluded and 49 articles included for the full text screening. Based on the full text screening 14 articles were selected as relevant. Most articles were excluded, because they did not assess indoor mould as defined by the in- and exclusion criteria (n=20). In unclear cases a mould expert was consulted (n=8). The other exclusion criteria are displayed in Figure 11.

**Figure 11: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram for the search of selected health effects on children due to mould**




***Study characteristics and quality assessment***

The systematic search yielded 14 articles eligible for the assessment. Eight of the identified reviews included meta-analyses.

The reviews used in summary at least 15 different databases to find suitable publications. Usually more than one database was included per review. The combination of the used databases varied strongly. The most reported databases were PubMed (n=9), Embase (n=6), Web of Science (n=4) and Scopus (n=4). The search included reviews that were published Jul 2010 to February 2021. The included primary studies mentioned in the reviews were originally published between 1950 and 2021.

Ten reviews included locations within the WHO European region, 7 reviews the WHO Region of the Americas, six reviews the WHO Western Pacific Region, two reviews Taiwan, two reviews New Zealand or Nigeria and one review Hong Kong, Egypt, USA, Canada, WHO South African Region, Brazil, Germany, India, Australia, WHO African Region or Jordan.

A risk of bias assessment tool was used in nine of 14 reviews. The most common tools used were funnel plot, Cochrane Collaboration guidelines and Newcastle Ottawa scales. Assessment of presence of publication bias was conducted in 11 publications, and a likely impact of publication or submission bias was addressed in 6 reviews.

### *Health outcomes and evidence*

The health outcomes were defined as doctor's diagnosis or were self- or parent-reported obtained by a questionnaire or an interview. Most reviews investigated the relation of exposure to indoor dampness or mould fungi/mould components and health effects on asthma (n=9), asthma exacerbations (n=5), wheeze (n=4) and/or allergic rhinitis (n= 5). Further health outcomes studied were infections of the lower respiratory tract, rhinoconjunctivitis, chronic rhinosinusitis, atopic dermatitis, eczema, itchy skin rash, itchy and blocked nose, allergic sensitization to inhalant allergens and general symptoms of the respiratory tract.

#### Asthma (manifestation, progression)

There was **consistent evidence** for a strong or an increased risk for developing asthma in six of the nine reviews (284–288). The OR tended to decrease with the higher age of the children. Tham et al. (289) found stronger relation of increased asthma symptoms with exposure to indoor fungi than to outdoor fungi.

Three publications found **variable outcomes** between exposure to mould and asthma (290–292). The results of these reviews are discussed later.

Three reviews reported **a consistent evidence** for a strong (286) or an increased risk (288) (OR 1.68; 95% CI 1.48–1.90); Fakunle et al. (292) (RR: 1.2, P=0.007) for wheeze.

#### Asthma exacerbations

There was **consistent evidence** for a strong or an increased risk for asthma exacerbations found in four reviews (284,287,290,293). **Limited evidence** was found by Dick et al. (188) and the results of Tham et al. (289) were inconsistent.

Sharpe et al. (290) reported a 34% to 51% increase of symptoms by increased fungal exposure by using random-effect estimates. Dick et al. (188) reported that the risk for asthma exacerbation was increased by 1.4 per 10-fold increase of outdoor or indoor fungal exposure. The exposure to mould showed a stronger association with asthma exacerbation than the exposure to dampness (289).

Caillaud et al. (284) conducted a systematic review of a systematic search of peer-reviewed literature including systematic reviews and meta-analyses, longitudinal, incident case–control and panel studies. 61 publications were included reporting visible mould, mould odour or quantitative assessment of culturable fungi or mould species. Adjusted OR were calculated separately for each type of study. The development and exacerbations of asthma were associated with visible mould and mould odour. The meta-analysis of longitudinal studies resulted in adjusted OR from 1.21 up to 9.08. The authors concluded that there is a **sufficient evidence** for a causal relationship.

#### Allergic rhinitis

There was **consistent evidence** for a strong or an increased risk for allergic rhinitis found in all five reviews that studied this health outcome (284,292,294,287,288).The OR, if reported, ranged from 1.12 to 5.1.

#### Lower respiratory tract infections (LRTI)

Fakunle et al. (295) conducted a meta-analysis of seven studies to investigate the association between exposure to microorganisms within the indoor environment and the risk of LRTI among children < 5 years. A stronger connection with the risk of LRTI was found with total fungal concentration [OR:1.27 (1.13, 1.44)] as a parameter (CFU/$m^3$), compared to visible mould spots [OR:1.20 (1.07, 1.34, P = .0010)]. The results of this meta-analysis have to be interpreted with caution, as the exposures were determined using different methods.

#### Dermal symptoms and atopic eczema

Interestingly, **no or little evidence** was found for a relationship of mould parameter with dermal symptoms or atopic eczema by the two reviews identified by our search (288,296). This was surprising, since based on epidemiological studies others have concluded **sufficient evidence** to support a link between atopic dermatitis and moisture damage/mould (282,297). One reason might be the low number of single studies of these health outcomes. Fisk et al (298) conducted a meta-analysis using four cross-sectional studies to

associate dermal symptoms to presence of dampness or mould in school environment. A part of the studies included both adults and children. [OR 1.13 (0.70, 1.83), P=0.38]. The authors considered the small number of studies and the high heterogeneity of the studies as main reasons for the weak evidence.

#### Further health outcomes

A strong association or an increased risk for respiratory symptoms generally was found in two reviews (292) and higher risk of lower respiratory tract infections (292) and increased cough in one review (296), respectively.

#### Microbial exposure

Fakunle et al. (292) suggested that increased microbial exposure was associated with an increased risk of respiratory symptoms [pooled relative risk [RR: 1.24 (1.09, 1.41), P=0.001]. The association was strongest with exposure to a combination of Aspergillus, Penicillium, Cladosporium and Alternaria species [pooled RR: 1.73 (1.30, 2.31), P=0.0002]. Stratified analysis revealed an increased risk of wheeze [pooled RR: 1.20 (1.05, 1.37), P=0.007 and allergic rhinitis [RR: 1.18 (0.94, 1.98) P=0.16] from any microbial exposure. On the contrary, a protective effect of microbial exposure against asthma was found in children under 5 years of age.

Concentration of extracellular polysaccharides, endotoxins or 1,3-b-D-glucans did not increase the risk of allergic health outcomes in children, or even had a tendency for a protective effect (288,292). Dust mite exposure alone was not related with asthma in children up to nine years, but there was evidence from observational and intervention studies reported by Dick et al. (293) that interactions between several exposures were important for asthma causation. Dust mite exposure is often closely related with mould damages (dust mites prefer humid conditions and feed on mould fungal spores/mycelia).

Lipopolysaccharides, a major outer surface membrane component present in almost all Gram-negative bacteria, increased the risk for lifelong wheeze significantly (OR 1.3) (293).

Most reviews not only analysed dampness and mould but also other indoor pollutants. 13 reviews provided specific information on the number of primary studies that included dampness and mould as pollutants. In one review the exact number of primary studies including dampness/mould as a pollutant was not clear (but at least there were four primary studies out of 84). The number of primary studies in the reviews that included outcomes of dampness and mould ranged from two to 61.

The definitions of exposure included amongst others water damage, damp stains, high air humidity or other dampness indicators, visible mould, mould spots, mould odour, endotoxins, beta glucans, elevated spore concentrations, occurrence of indoor mould related fungal genera and species. The exposure was most frequently investigated by experts or was self- or parent-reported by the occurrence of visible mould (n=11) or signs of dampness (n=5), mould odour (=4) or occurrence of a water damage (n=2).

Various methods were used to assess mould exposure. The occurrence of mould or mould-related components in the reviews were determined with self-report questionnaires, inspections by trained persons or experts. The most recent studies included more specific parameters such as identification and quantification of fungal species, or measurement of mould components such as (1, 3)-β-D-glucans (299,300), extracellular polysaccharides, and PCR based detection (301,302), and quantification methods from air or dust samples (303,304).

Visible mould or mould spots are the easiest parameters to detect mould damages. However, visible mould without a validation by other methods such as microscopy or molecular methods, is a highly subjective parameter. Other stains on surfaces can be mistaken for mould and vice versa. Another problematic issue is, that visible mould is differently defined by the authors of the studies. For example, Hurraß et al. (282) refer visible mould as mould stains on all surfaces, including hidden damages. Self-reported visible mould however refers to (presumed) mould stains on surfaces on the room side.

There is a large amount of hidden mould damages in building structures, which represent about half of the estimated mould damages (305). Therefore, studies might underestimate the number of children exposed to mould.

Mould odour is often used as a parameter for mould damages. The advantage of this parameter is that it represents both visible and hidden mould damages. However, it is a highly subjective specification, as far as microbial volatile organic compounds (MVOC) are not measured. Mould odour was associated with various health outcomes such as rhinitis and subcategories of allergic rhinitis (294) and increasing risk of developing asthma (291). The results of both reviews show that mould odour was a surprisingly good indicator of a mould damage and often presented a good or even stronger association to health outcome than visible mould or other exposure parameters. However, it remains unclear whether other exposures might play a role for asthma and rhinitis, including house dust mites and chemicals emitted from damp materials. Jaakkola et al. stated, that dampness as such was related to increased risk of rhinitis outcomes, too (294). It should be noted that in the review by Jaakkola, also adults were included in the subject group.

The association of the reported mould odours and the health outcomes suggest that hidden mould damages have a relevant negative impact on health. Hidden mould can release substances into indoor air that were not measured in the present studies or cannot be detected in air or dust samples using the methods currently available.

Methods that measure the concentration of fungal species particles/substances related to mould damage are mainly conducted by experts and are therefore less frequently used in studies including high numbers of households/participants.

The concentration of the fungi/bacteria were often measured from air samples (n=4 reviews) or dust (n=3 reviews) and the quantification of the microorganisms were mainly based on cultivation of the mould fungal/bacterial species. Because of the selectivity of the cultivation (culture medium and incubation temperature used), the total number of fungal/bacterial species in air or dust is probably higher than the measured concentrations. In fact, one should keep in mind that not all moulds and bacteria can be cultivated at all in laboratory settings. The mould fungi were usually identified to genera level and in particular cases to species level. The fungal genera that were most frequently recorded include both outdoor and indoor-related fungal species.

Four reviews (286,288,292,294) included studies with the measurement of other microbial compounds such as fragments of the cell surface of mould fungi or bacteria (1, 3)-β-D-glucans, extracellular polysaccharides and endotoxins). Hereby (1, 3)-β-D-glucans were not correlated with a higher risk of any respiratory health symptoms.

#### *Discussion*

There is **reliable evidence** for a number of health outcomes of the respiratory tract including development of asthma, exacerbation of asthma, allergic rhinitis and wheeze in children exposed to mould. The results agree with the causal relationships reported by Hurraß et al. (282) and Kanchongkittiphon et al. (47). Furthermore, there is at least **suggestive evidence** for the association between exposure to mould and increased number of respiratory tract infections in children.

Mould exposures tend to be stronger associated to health outcomes than dampness, and indoor mould-related fungal species tend to lead to more severe health outcome than outdoor related species.

#### Asthma (manifestation, progression)

There was **consistent evidence** of positive associations between dampness/mould exposure and asthma development as well as exacerbation of asthma symptoms. These results support the conclusions of causal relationship with asthma and its exacerbation (47,282). Here, only the studies with more uncertain associations are discussed.

The statistical analysis of mould related health outcomes is often affected by the high heterogeneity of the studies regarding sample size, age ranges, outcome definitions and methods used to measure exposure. The heterogeneity might explain some of the inconsistent findings. Sharpe et al. (290) reviewed the associations of health outcomes with specific mould related fungal genera or species. All in all, 17 studies were included in the analysis. Depending on the statistical model and exposure setting used, the results varied from no association with total fungal count to 51 % increased risk for asthma symptoms. Also, Simons et al. (291) reported variable relationships between asthma symptoms and moisture or mould.

Odds ratios for moisture varied from <1.00 to 1.16 and for mould from <1.00 to 2.44. These results were based on two studies, that differed in study design and measurement method of the exposure used. Mould in bedroom by case-control study was conducted by Martel et al. (306) vs. mould odour and visible mould in a cohort study by Jaakkola et al. (307).

The lack of longitudinal studies makes it more difficult to evaluate a possible causal relationship between mould and the health outcomes.

Sharpe et al. (290) reported a 2-fold higher risk of higher rates of infant wheeze and for developing asthma in children and adults in a presence found of fungal genera Aspergillus and Penicillium. Both genera include common indoor mould species. However, due to the low number of studies that identify mould fungi to genera-, or species level, the results were based on only two longitudinal studies (308,309). In addition, the results of Fakunle et al. (292) were based on two longitudinal studies (310,311). They conducted a random-effect meta-analysis to estimate the relationship of health outcomes with specific mould-related fungal genera or species and also specific microbial agents in low versus high concentrations. A higher risk for respiratory symptoms in general by increasing microbial exposure [pooled relative risk (RR): 1.24 (1.09, 1.41), P = 0.001], was found.

Exposure to specific microbial agents such as endotoxins had a protective effect against asthma [RR: 0.78 (0.62, 0.99), P = 0.04]. This is in accordance with studies, that show that microbial exposure, especially in young age, can have a protective effect. Also, an environment with a diverse microbiome, such as farm environment can be beneficial on children´s health (312,313).

The role of microbial agents for different health outcomes and also the prevention of allergic diseases should be further investigated. The microbiome of the human body as well as the indoor- and outdoor environment needs to be studied in much further detail to detect the protective as well as the negative health effects.

#### Asthma exacerbation

The results demonstrate that there is an increased risk of asthma exacerbation in children by mould fungi. A few studies suggest a dose-response relationship for triggering or exacerbation of asthma in children by mould fungi, especially by genera Alternaria, Penicillium and Cladosporium (290,292,293).

Dick et al. (293) demonstrated that the risk for asthma exacerbation was positively correlated with the fungal concentration. However, the results were based on two studies and overall, a limited evidence for the association between exposures to moulds and asthma exacerbation was found. The intervention study included, was conducted with a rather high age range (2-17 years) and had a small sample size (n=62), which might have affected the results. The second included study was an observational study (n=936) that measured the concentration of mould fungi in the homes of asthmatic children on five occasions within two years. Due to the low number of measurements and a high seasonal variability of the concentrations of outdoor-fungi, usually used as a reference to the indoor fungal concentrations, the strength of these results might be limited. Also, Sharpe et al. (290) showed in a review and a meta-analysis of 17 studies a positive relationship between the fungal concentration and asthma symptoms in children and adults. The presence of Cladosporium, Alternaria, Aspergillus, and Penicillium species increased the risk of exacerbation of current asthma symptoms by 36-48% and general fungal exposure by 34-51% compared with children exposed to lower concentrations of the fungi.

Sensitised and asthmatic children are susceptible to asthma exacerbations also through outdoor fungal exposure. Tham et al. (289) conducted a systematic review of 15 studies to examine the role of outdoor fungi in asthma exacerbations in childhood. Outdoor fungal exposure was related with increased asthma symptoms, whereas indoor fungal exposure played a stronger role than the exposure to outdoor fungi. Comparable to the analysis by Dick et al. (188) with an inclusion of children up to 17 years, the age range of the children was high (<18 years) and the findings were not consistent.

It was assumed that theoretically all mould fungi could have a certain allergic potential (Wiesmüller et al., 2017), however, all in all fungi seem to have a rather low sensitizing potential compared to other allergens. Sensitizing prevalences of 3–10% in the general population across Europe have been found (282). The

results of this review suggest that the allergic potential of the mould fungi and the severity of the asthma symptoms vary between different fungal species. More research on the role of fungal diversity and further allergenic mould fungi is needed.

Allergic rhinitis as well as wheezing can be precursors of asthma in childhood but also of asthma which develops later in adult life (314). The origin can be an allergic sensitisation acquired during childhood that becomes or stays clinical later in life (315). Therefore, preventive measures protecting children will also prevent diseases when these people become adults.

### The role of ambient humidity

Ambient humidity can affect the indoor environment and be linked with dampness related exposures in indoor environments such as mites and mould.

Gao et al. (316) found in their systematic review, that the ambient relative humidity increased the risk for development of asthma. An increase of 10% relative humidity resulted in 31% higher probability of developing asthma in the childhood, and increased asthma symptoms, allergic rhinitis, wheezing. However, regarding humidity, some studies found opposite health effects

In summary, the results of the selected reviews and meta-analyses published between 2011 and 2021 demonstrate, that children can be susceptible to dampness and mould in the indoor environments. Associations between dampness or indoor mould exposure and various health outcomes, such as asthma, asthma diagnosis or exacerbation of asthma symptoms, allergic rhinitis and wheeze were found.

The precautionary principle and prompt professional renovation of water- and mould damages are needed to prevent adverse health effects of dampness and mould in children.

### Strengths and limitations

The identified studies on mould related health outcomes have a high heterogeneity regarding sample size, age ranges, outcome definitions and methods used to measure the exposure. Additionally, On the other hand, mould infestations are highly variable and divers regarding the microbial community and bioaerosols that can occur. For epidemiologic studies these  are big problems because under these circumstances the exposure cannot be  addressed in a consistent way. Beyond that, Asthma and allergic diseases are very often firstly not easy and clearly to diagnose and secondly it is often very difficult to find the causative agent. The association of the exposure and symptomsdoes not necessarily imply causation. These reasons might have led to **inconsistent findings** and lower statistical strength of the associations. Under these premises a concise table on the strongest effect associations is not feasible, the highest reliability for consistent effects applies for asthma and the exacerbation of asthma.

The measurement methods for mould exposure used in the studies vary widely in their informative value and ability to detect mould infestation. For example, it is known, that mould fungal spores are not always released to the indoor air, especially from hidden damages. Therefore, the use of air samples for investigation of the exposure might lead to false negative results. Furthermore, the validity of microbial measurements depends strongly on the quality of the sampling. Therefore, skilled samplers, as well as standardized sampling strategies and methods (such as ISO 16000-19: 2012 and ISO 16000-20: 2014) are recommended for future studies.

Furthermore, little is known about the effects of mould on the health of children overall. Children are generally a very healthy part of the population. Children are often not yet sensitised towards certain mould species. On the other hand, protective effects of microbial exposure might occur, because the developing immune system might benefit from being challenged with contact to microbes and their compounds (312). Therefore, health effects like allergic diseases are rarely found consistently – especially because some microbiological exposures are also preventing allergic disease. Because the determination of the mould exposure is challenging, and the modes of actions are not well understood yet, it is very difficult to gain insight in the -mould-specific aetiological origins of reported health effects on children.

Only few longitudinal studies on the relation of mould damages on health outcome were included in the reviews. The lack of longitudinal studies makes it more difficult to evaluate the health outcomes.

Therefore, further longitudinal studies of health outcomes in individuals exposed to mould are needed. To gain better understanding about the health effects of exposures caused by mould infestation, the exposure should be addressed in greater detail. It would be very helpful if in the future consistent methods for determining mould infestations were on hand. Modern biochemistry methods like gene or protein analytics can be helpful in future studies to determine a more exact spectrum of mould and bacteria species in the environment. Activities in harmonising these methods would be of utmost importance. The same accounts for the definition and classification of related symptoms as to date allergies, onset of asthma, wheezing, atopy, rhinitis and exacerbation are all entangled and not clearly distinguishable.

For these reasons this umbrella review (as the regarded underlying reviews as well) cannot deliver stronger evidence or even more insights into such complex exposure-effects relationships (like when it comes to mould-effects in children) – except that to date their assessment is still very challenging and the scientific landscape concerning this topic is still developing.

Certainly, this does not mean, that preventive measures are not needed as the overall trend in literature is strongly pointing in the direction of harmfulness of mould infestations in children (and adults).

More work is needed to assess the occurrence of mould infestations, too. For example, in Germany, on average 5-15 % of the households have a visible mould damage. In addition, further 14 % of German households are likely to have a hidden mould damage (305). We recommend that future studies consider a combination of different measurement methods for microbial exposure. A combination of molecular and epidemiologic methods as well as methods that allow conclusions about the non-visible damages in the building structures such as support by a building expert and/or high-quality mould detection dogs, could improve the results.

The significant increasing risk for wheeze caused by lipopolysaccharides, reported by Dick et al. (293) might indicate, that besides mould fungi, bacteria are a relevant health risk by a mould infestation. However, parameter of bacterial activity in mould damages, such as lipopolysaccharides, endotoxins or culturable bacteria were rarely measured, therefore it is not possible to make conclusions of their possible health risks. More studies about the role of bacteria commonly detected in mould damages, such as actinobacteria, should be conducted, preferably with methods that allow an identification (commonly at genus level) through cultivation and/or molecular analysis.

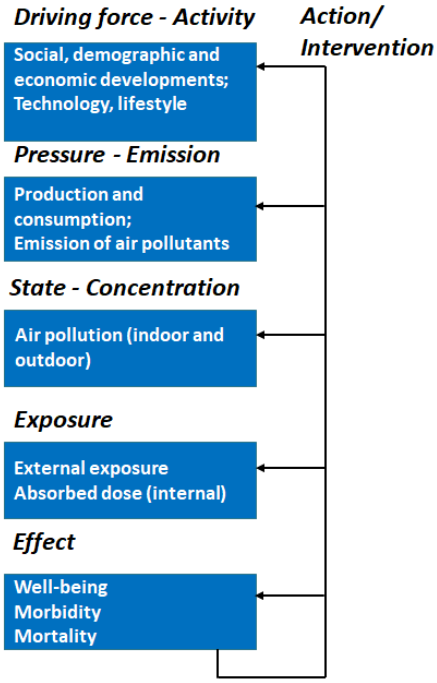
The role of microbial agents and their combinations for different health outcomes and also the prevention of allergic diseases should be further investigated. The microbiome of the human body as well as the indoor- and outdoor environment needs to be studied in much further detail to detect the protective as well as the negative health effects.

## 3.3 Intervention studies

### *3.3.1 General introduction*

Within this section evidence is gathered on interventions to control the health impact of air pollution, with a focus on children and adolescents. Interventions can be taken in different steps from the DPSEEA framework which links driving forces to health effects through different steps: driving force – pressure – state – exposure - effect – action (Figure 12)(317).

**Figure 12: Driving force – Pressure – State – Exposure – Effect – Action (DPSEEA) Framework**




Within the DPSEEA conceptual framework, drivers are the social, demographic, technological and economic developments in societies and the corresponding changes in lifestyles. The production and consumption of goods through human activities, exerts pressure on the environment, e.g. in the form of gases and particles emitted in the air by various sources. This leads to changes in the state of the environment, leading to e.g. poor air quality both indoor and outdoor. Individual exposure to these environmental challenges is influenced by factors such as human behavioral and lifestyle choice. The exposure may give rise to various health effects, including both physical and mental outcomes. Interventions can take place in the different steps of the DPSEEA framework:

- A change in a driving force or activity (e.g. policies on the development of clean air zones, technological advancements), can result in a decrease in air pollution emissions putting a pressure on the environment. The European ambient air quality standards and laws regulating emissions of air pollutants, are examples of guidance that force national or regional governments to take interventions to reduce polluting activities.
- A decrease in emissions (pressure), can result in improved ambient air quality (state). The step from emissions to concentrations is heavily influenced by meteorology (affecting the dispersion and chemical processes of pollutants in the air as well as deposition) and local circumstances (e.g. general pollution levels, urban or housing configuration).
- A decrease in concentrations (state), can result in a decrease of exposure and inhaled dose. Individual avoidance of exposure depends on time-activity patterns in relation to indoor and outdoor air quality. The uptake and retention in the body depends on personal parameters.
- A decrease in exposure and dose, can result in improved human health conditions (effect). The health response is determined by individual susceptibility factors, physiologic mechanisms of damage and repair.

According to a recent review of interventions to improve outdoor air quality and public health by Public Health England, the hierarchy for the most effective interventions is to first reduce emissions, then reduce concentrations and then reduce exposure (79). The review provides local practitioners and policymakers with an indication of the broad range of available interventions across 5 focal areas: transport, spatial planning, industry, agriculture, people's behaviour. Table 87 provides an overview of interventions in the areas transport, spatial planning and people's behaviour that provide multiple potential benefits for outdoor air quality and public health outcomes.

**Table 87: Public health evaluation overview of interventions with multiple potential benefits for air quality and public health outcomes for the focal areas behaviour, planning and road transport, based on Public Health England (79). Columns 3-6 indicate the interventions have been considered in the current report**

| **Intervention category based on Public Health England** (79) | **Intervention as defined in Public Health England** (79) | **Clean air zones** | **Siting and commuting** | **Design** | **LEZ** |
|---|---|---|---|---|---|
| Behaviour | Exposure reduction programmes | | x | | |
| | Eco-driver training | x | | | |
| | Public engagement | x | x | | x |
| | Investment in public transport | | | | |
| Planning - motorised transport | Co-implementation of various measures | x | x | x | |
| | Driving restriction | x | | | x |
| Pollutant removal | Green infrastructure - urban vegetation | | | x | |
| Road transport - reduce emissions from existing vehicles | Promote walking and cycling | | x | | |
| | Promotion of low emission zones | | | | x |
| | Promote abatement retrofit | | | | |
| | Increase fuel duty/target at diesels | | | | |
| Road transport - reduce demand for more polluting forms of transport | National road pricing / congestion charge | | | | x |
| | Provision of school buses | | | | |
| | Subsidising public transport | | | | |

In this chapter we focus on public health interventions that can be taken by local or national authorities specifically targeting to reduce the health effects of children and adolescents due to air pollution in the outdoor and indoor environment.

Children and adolescents spend time in different microenvironments: home, school, indoor and outdoor activities not at home nor at school, transport. A review by Osborne et al. (3) gathered evidence on concentration and exposure in school environments. They observed that the home-to-school commute often results in significant exposure to air pollution, especially for traffic-related pollutants such as black carbon, UFP and $PM_{2.5}$. Pollution peaks are also encountered at school gates, drop-off zones and in school playgrounds (3). This observation also followed from recent studies carried out in Milan and Barcelona where the highest dose/time intensity was measured during the commute (1,2).

We describe the effectiveness of potential interventions affecting air quality in indoor and outdoor school/childcare environments including the school commute, as well as in the home environment. We focus on interventions of which the effectiveness has been proven by measuring or modelling. The effects can take place in one or several steps of the accountability chain activity-emission-concentration-exposure-dose-health shown in Figure 12. As will be described below, the effectiveness of interventions, in terms of improved air quality, reduced exposure or improved health outcomes, is often not evaluated

(3,318). The use of impact evaluations or before-after comparisons through longitudinal studies can provide valuable information on its effectiveness (319).

At EU level, no guidance is available for interventions to improve air quality in the school environment. U.S. EPA has developed a guidance for school personnel, students and parents concerning best practices for reducing near-road pollution exposure at schools (320).

For schools in urban areas where traffic is a significant source of air pollution, epidemiological research carried out within the BREATHE project led to a list of interventions to improve air quality in schools (2):

- Promote active travel or public transport to commute to school;
- Reduce traffic in school surroundings, increase greening;
- Clean and replace sand from the playgrounds periodically;
- Move schools or classrooms away from traffic.
- Clean the classrooms after school hours (opening the windows) and select a 'green' cleaning product;
- Raise awareness within and outside the school community of impacts on children's and public health of air pollution and spread measures to reduce the use of private cars.

The interventions involve school personnel, pupils and their parents, urban designers and transport planners. The authors mention that at the time of publishing there were no studies assessing the effect of the proposed interventions (2).

The concrete development, implementation and success of interventions often depends on local circumstances, as the different steps in the activity-emission-concentration-exposure-dose-health accountability chain are heavily influenced by meteorology, local circumstances and individual behaviour. This makes it difficult to deduce a general assessment of the effectiveness of air quality interventions. However, general principles can be included when developing local plans to improve local air quality.

We describe different interventions separately, but it is recommended to combine them in a coherent approach involving all sectors involved: transport, spatial planning, environmental and public health (79). The interventions are likely to act cumulatively to produce significant changes in air quality and exposure and eventually health. In addition to air quality improvements, many actions are likely to bring multiple public health benefits such as e.g. increased physical activity and community cohesion.

The identification of the intervention studies discussed below is described in section 2.2. We consider four interventions affecting ambient air pollution and three interventions targeting indoor air pollution:

- Installation of clean air zones around schools;
- Siting of schools, commuter mode and route;
- Design of schools;
- Low-emission zones;
- Indoor air quality in schools: ventilation and other measures to decrease exposure to air pollutants;
- Reduction of second hand smoke exposure;
- Smoking bans.

For the interventions targeting ambient air pollution, we indicated the overlap with the interventions defined by Public Health England (79) in Table 87.

In the following sections selected features have been assessed for every intervention type:

- Intervention characterization and overview of current interventions
- Study search and selection
- Study characteristics and quality assessment
- Changes in activity, emissions, concentrations, exposure and health outcomes and evidence
- Discussion
- Research gaps and future research

The search criteria are shown in Appendix A, the scanned references in Appendix B, and the detailed results of the screening in Appendix C.

### *3.3.2 Clear air zones around schools*

#### *Intervention characterization and overview of current interventions*

In the review by Osborne et al. (3), proximity to nearby roads, traffic density and traffic flow, have been identified as key factors influencing concentrations on school grounds. Several studies indicated that drop-off points around schools have high ambient concentrations of traffic-related pollutants. School playgrounds can contribute significantly to inhaled dose as children's activity levels and inhalation rate in playgrounds tends to be high. Hence the creation of a clean air zone around schools by decreasing emissions from motorized traffic, results in a decrease in children's exposure.

This can be realized by implementing no-idling zones in the neighbourhood of schools (and other areas with vulnerable population), this intervention has also been promoted by Public Health England (PHE) as part of eco-driving interventions. They state that eco-driving (including improved driving behaviour and reduced engine idling time), smooth driving and speed reduction can reduce fuel consumption and potentially pollutant emissions (79).

Another possible intervention is to relocate drop off/pick-up points away from school entrances, as also suggested by An et al. (318). During drop-off hours cars are often queuing at these points, in a recent study the concentration of $PM_{2.5}$ was found to intensify by approximately a factor of three (321).

Ultimately the installation of a school street in a (section of a) road near a school entrance, creates a pedestrian and cycle only zone in front of the school, as there is a temporary restriction on motorised traffic during school drop-off and pick-up times. The concept of a school street was initially launched in 2009 in Bolzano as a measure to increase traffic safety around the school (322) . Currently school streets are being implemented in many school environments in different European countries. The ban of motorized traffic near the school entrance is expected to decrease the traffic-related emissions at the drop-off points and possibly at the school playground if sited next to a road.

#### *Study search and selection*

##### Eco-driving intervention

As described in section 2.2.5 a PubMed search was performed on anti-idling interventions, yielding 9 hits. These hits were screened using the methodology by Public Health England (79). This resulted in the inclusion of 3 studies.

##### School street intervention

There is a lot of practical information and guidance available online for local authorities on how to establish a school street. However, school streets are a largely undocumented intervention measure in scientific research in the English language. The major information can be derived from local authority reports on planning or implementing school streets. A PubMed search was performed on school street interventions, yielding 0 hits. A Google search yielded different hits, however only one study was included as the effectiveness of a school street has not been assessed in all other studies.

#### *Study characteristics and quality assessment*

##### Eco-driving intervention – anti-idling

A US study by Ryan et al. (323) determined the impact of an anti-idling behavioural campaign for school bus drivers on outdoor air quality at four schools with varying levels of bus and automobile traffic. They measured traffic-related air pollution concentrations in a pre- and post-intervention setting (323).

Mendoza et al. (324) studied two anti-idling behavioural campaigns in schools in Utah (U.S.) to study the effect of reduced engine idling on traffic-related air pollution exposure.

An Australian study (325) demonstrated the effectiveness of an anti-idling behavioural intervention targeting parents at primary schools. Based on two focus group discussions with parents, a low-intensity 4-week anti-idling intervention was developed, comprising onsite signage, four newsletters, and two fact

sheets. Exposure to selected air pollutants was assessed during pick-up and drop-off times pre- and postintervention at 12 randomly selected independent schools (10 intervention and 2 control) across the Perth metropolitan area (325).

#### School street intervention

In a recent literature review by Davis (326), 16 studies and reports on the implementation of school streets have been used to assess the impact of school streets on mobility safety issues in the school environment (326). The studies were mainly pre- and post-intervention assessments by local authorities, none of them had been peer reviewed. The evidence from the literature was supplemented by a number of semi-structured telephone interviews with officers responsible for local authority school streets.

In a Flemish study (327), the effects of five school streets of primary schools (pupils 6-12 years) have been assessed in a pre- and post-intervention setting. The effects on mobility, air quality and noise, health, perception and wellbeing have been investigated.

### *Exposure and health outcomes and evidence*

#### Eco-driving intervention – anti-idling

In the four US schools, reductions in $PM_{2.5}$, elemental carbon and particle number concentration have been observed following an anti-idling campaign for school buses. The largest differences were observed at the school with the greatest number of school buses. No assessment of emissions, exposure nor health outcomes has been performed in this study (323).

Following an anti-idling campaign Mendoza et al. (324) found a 38% decrease in idling time and an 11% decrease in the number of vehicles idling at the school drop-off zones. The air quality measurements showed improvement in the middle of the campaign, but seasonal variability as well as atmospheric inversion events had substantial effects on overall ambient pollutant concentrations.

The Australian study results showed that a low intensity behavioural intervention can be an effective strategy to affect parents' attitude towards vehicle idling. This was demonstrated by the reduced number of idling vehicles observed in 8 of the 10 intervention schools and decreased overall particulate matter concentration after the anti-idling intervention (325).

#### School street intervention

Changes in activity. In the studies assessed by Davis, in almost all cases the total number of motor vehicles across the school street and neighbouring streets were reduced (326). This is also the case in the five Flemish schools, where motorized traffic in the school environment was reduced by 30% during the closure of the school street, but also with 6% during the entire day (327).

Davis found that active travel levels increased at the streets with school streets (326), this was also observed in the Flemish schools. In the latter analysis questionnaires revealed that the shift of passive to active transport increased with age, mainly the older children (10-12 years) biked or walked to school instead of taking the car (327).

Changes in emission. No assessment of changes in emissions has been performed for this intervention type.

Changes in concentration and exposure. A pre/post analysis of measured air quality levels showed a positive effect (i.e. a decrease) of the school streets on the concentrations of three traffic pollutants: nitrogen oxides, black carbon and ultrafine particles. The effect was limited in time, occurring only during and shortly after the school street closure period, and limited in place, occurring in the car-free area. No detailed analysis of indoor air quality in the classrooms has been performed, the air pollution levels were mainly determined by the type of activity in the classroom (328).

Changes in health outcomes. Active commuting to and from school has been associated with higher physical activity levels (329). As mentioned before the installation of a school street resulted in an increase of active transport to school. However, the school streets in the Flemish study had no significant effect on the daily physical activity (moderate-intensity and vigorous-intensity) level of the school children (330).

Positive health effects were observed on airway parameters (decrease in inflammation parameter (exhaled NO) and increase in airway elasticity), with varying results for the different schools (330). No effects were measured for cardiovascular parameters (blood pressure, heart rate, micro vascularity of retina) (330).

Changes in attitude and perception. In the literature review by Davis the school streets are supported by the majority of parents and residents living on the closed and neighbouring streets, their support increases after any trial period (326). In the Flemish schools the school street was positively assessed by most parents in terms of safety, accessibility, child friendliness, annoyance of air pollution and noise (327).

***Considering the setting (if possible)***

In the anti-idling behavioural intervention focusing on bus drivers, the effects on air quality were largest for schools with most buses (323).

It was found in the Flemish study that the positive impact of a school street on air quality is highest in school streets where the local air quality is dominated by traffic emissions (328).

In a recent study on the impact of car-free days and events on the environment and human health, it was stated that car-free events require intensive planning to be successful (319). The impacts of car-free events are highly variable and seem to depend on the scope (frequency, duration, and geographic size) and goals of each car-free event. The organization and execution of car-free events, as well as public support and stakeholder engagement, greatly influence the level of success and the sustainability of such initiatives (319).

***Discussion***

Anti-idling behavioural interventions can have potential benefits for local air quality in a school setting as they reduce emissions in pollution hot spots of drop-off zones often in the neighbourhood of the school gate and playground where children are playing during drop-off and pick-up times. Stationary vehicle idling could also be addressed by enforcement e.g. in the neighbourhood of schools, childcare facilities, hospitals, etc. as suggested by Public Health England (79).

The installation of a school street, a traffic ban at the start and end of the school day in the immediate vicinity of the school temporarily, reduces the exposure of pupils to traffic-related air pollutants during dropping-off and picking-up hours. Depending on the location of the playground, ambient air quality is also improved there. The installation of a school street promotes active commute and hints at positive respiratory health effects. An expansion of the school street concept both in time (entire school day) and in space (larger traffic-free zone) is expected to result in larger and longer improvements in air quality. A school street requires fewer parking lots in the immediate vicinity of the school, these spaces can be unsealed or greened and be used for recreation. It is advised to start a school street in a test setting to explore the impact on residents and merchants living on the closed and neighbouring streets.

The evaluation of anti-idling interventions was carried out for a US car and bus fleet composition, which differs from the current situation in Europe. However, following their approach and assumptions regarding fleet composition and similar reductions in idling, the effect on emissions can be estimated in a European context.

In the Flemish study (328), the impact of a school street was assessed three weeks after its introduction, after this period the perception and attitude by children and their parents was positive. However, it would be of interest to measure the change in behaviour (active transport to school) and other parameters after a longer evaluation period.

The review by Osborne et al. (3) and the study by Rivas et al. (2) both stress the importance of personal monitoring in future research. In some studies, personal concentrations are considerably higher than those measured by static monitors because of time-activity patterns. Air quality modelling can predict exposure at home and school well, but not for commuting (2,3).

As mentioned already before, future research could be most useful if it focused on measuring health outcomes associated with car-free events through longitudinal studies (319).

### 3.3.3 Siting of school and childcare facilities and commuter mode and route

#### Intervention characterization and overview of current interventions

Infants and children spend considerable time at childcare facilities, kindergartens or school . From a precautionary point of view, it is important that their buildings are in the least polluted locations. Osborne et al. (3) identified proximity to nearby roads, traffic density and traffic flow as key factors influencing concentrations on school grounds in several studies.

At EU level no specific policies or regulations are in place to regulate the location of schools and childcare facilities in relation to environmental hazards. In some European countries and cities guidance and policy are in place to regulate siting of new schools and childcare facilities to prevent exposure of children to air pollution. These guidelines or laws are based on indicators such as distance to pollution sources or air quality levels.

The indicator 'distance to pollution sources' can be interpreted qualitatively. As an example, in the city of Berlin the Pollution Control Law ensures sufficient distance between sites where vulnerable groups reside (e.g. schools, care homes, hospitals) on one hand, and industrial locations as well as traffic sources on the other hand (331,332). However, it is not specified how long a sufficient distance is.

The indicator 'distance to pollution sources' can also be interpreted quantitatively, such as in the Netherlands where local air quality levels are included in the assessment(333). The Decree on sensitive destinations (e.g. schools, childcare facilities, etc.) defines 'research zones' within 300 and 50 meters of motorways and provincial roads, respectively. Within the research zone the total number of people belonging to a 'sensitive destination' may not increase if the limit values for $PM_{10}$ or $NO_2$ are exceeded or are at risk of being exceeded. In the U.S. state of California, the Air Quality and Land Use Handbook recommends that new schools are not located within 500 feet (approx. 150 m) of major roadways, some districts within California use a more stringent distance of 1000 feet (320) .

However, low pollutant concentrations are not the only factor to consider in selecting locations for schools. The location of a school influences the primary modes of travel to and from school (318). School sites at sites with better cleaner air quality are often further away from housing areas, and therefore require commutes using motorized transport. This potentially leads to higher exposure levels during commuting compared to walking or cycling to a school located in the neighbourhood of their house. Hence, from a health exposure perspective, siting schools away from high-volume roads within a walkable distance from home is ideal (318).

In the UK, the NICE (National Institute for Health and Care Excellence) review for the development of the guidelines on Transport Related Air Pollution (TRAP), evaluated planning development control decisions and interventions (334). The NICE guidance comprises the above-mentioned aspects:

- Minimise exposure to vulnerable groups by not siting buildings (such as schools, nurseries and care homes) in areas where pollution levels are / will be high (also here, no exact air quality levels are provided);
- Design and site new developments such that the need for motorized travel is reduced.

I the US, School Siting Guidelines by U.S. EPA recommend considering many factors in the selection of locations for new schools. This includes proximity to the community and distance from roads, accessibility by walking or biking, and exposure to air pollutants during student commutes (320).

A literature review on air pollution exposures for the general population (no focus on children) in travel microenvironments in Europe showed the highest exposures in car drivers and lowest exposure in pedestrians (335).

#### Study search and selection

##### Siting of schools, commuting route and mode

As described in section2.2.5, a PubMed search was performed on interventions related to siting of schools, commuting route and mode, yielding 14 hits. These hits were screened using the methodology by Public Health England (79). A Google search yielded one extra study. This resulted in the inclusion of 4 studies.

### *Study characteristics and quality assessment*

#### Siting of schools

As mentioned above, few review articles have examined the effect of traffic pollution mitigation measures (3,318). To our knowledge, no scientific literature is available on interventions where the health of the school children was assessed when changing the site of their school or childcare facility. The effect of school siting on commuting mode and hence exposure of children during commuting was studied by Wolfe et al. (336). They modelled the dynamic exposure of children due to traffic-related air pollution for children attending school in two different environments. One school was in a high-traffic environment within 150 meters of a major road and in the vicinity of children's home, children were walking to this school. The other school was in a low-traffic, cleaner air quality site, children commuted on average 19 km via private transport to this school. The time-weighted exposure was composed of exposures to $PM_{2.5}$, benzene in different micro-environments: commuting, (un)loading at school and at school (336). They only considered contributions from roadway sources.

As school siting impacts the commuting mode and route, we also discuss interventions that have been proven effective to consider a healthy commuting mode and route.

#### Commuting route and mode

In a UK-study, Dirks et al. (337) quantified the air pollution exposure experienced by children walking to school and those being driven by car. Three (adult) participants measured personal exposure to ultrafine particles (UFP): one adult travelled to school by car, the other two walked, but on opposite sides of the road for the majority of the journey.

The effect of a walker's route choice on their exposure to UFP on the walk to school has been assessed in a New Zealand by Rafiepourgatabi et al. (338). During morning commutes over a period of three weeks, exposure to UFP was measured along three routes: two routes were alongside both sides of a busy arterial road with significantly higher levels of traffic on one side compared to the other, and the third route passed through quiet streets (the background route).

Ahmed et al. (339) performed and evaluated a route to school informational intervention. They targeted parents/guardians of school children in Antwerp, Belgium to adopt school routes with low air pollution exposure.

### *Changes in activity, emissions, concentrations, exposure and health outcomes and evidence*

#### Siting of schools

Changes in activity. The siting of schools influences the transport mode to school and the associated exposure. Wolfe et al. (336) assumed that children attending school in a nearby school in a high-traffic environment, were walking to school and children attending school in a further away low-traffic environment, commuted via private transport to a school.

Wolfe et al. (336) did not evaluate changes in emissions for commuting to the school environments considered. Under the assumption of children walking to a school in a high-traffic environment and children commuting via private transport to a school in a low-traffic environment, Wolfe et al. (336) modelled a lower exposure for the walking group for traffic-related air pollutants ($PM_{2.5}$, benzene, elemental carbon (EC)). The major contribution from the exposure due to traffic-related air pollutants comes from the transport to and from school as well as the (un)loading at the school site (336). Wolfe et al. (336) did not assess health outcomes. In a guidance document on mitigating exposure to traffic pollution in and around schools, Kumar et al. (321) encourage walking to/from school for the benefit of mental and physical wellbeing and to support independence, social skills and road safety skills for children, as well as to reduce traffic volume/congestion and air pollution. Regular walking to/from school can also strengthen children's sense of community and understanding of their local area (321).

#### Commuting mode and route

Results of the study by Dirks et al. (337) suggest that car commuters experience lower levels of air pollution dose, compared to people walking, due to lower exposure and reduced commute times. This is in contrast

with the literature review by de Nazelle et al. (335) and the above-mentioned study by Wolfe et al. (336), where greatest exposures were found in car drivers and lowest in pedestrians. This is probably due to the fact that in the review and in the study by Wolfe et al. (336) cars and pedestrians were taking different routes and different commuting times, while in the study by Dirks et al. (337) the same route was considered. Dirks et al. (337) suggest that the largest reductions in exposure for pedestrians can be achieved by avoiding close proximity to traffic queuing up at intersections, and, where possible, walking on the less congested side of the road, especially during the morning commuting period. Major intersections and bus roads should also be avoided as they were associated with peak exposures (337). These suggestions were evaluated in the New Zealand study, which found that the mean exposure for the pedestrian walking along the background route was half the exposure experienced on the other two routes. Walkers on the trafficked side were exposed to elevated concentrations 2.5 times longer than the low-trafficked side. However, the duration of the elevated exposure for the background route was close to zero (338).

The route to school informational intervention indicated that 60% of the participants could benefit themselves by adopting the suggested cleanest routes to school, based on $NO_2$ concentrations between the alternative and current routes. After being informed that alternative school routes could result in a decrease in $NO_2$ exposure, 77% of study participants changed their routes (339).

#### *Discussion*

In the siting of schools and childcare facilities it is important to keep the exposure from mainly traffic-related air pollutants as low as possible. No interventions on the influence of siting were evaluated, but the consequence of relocation such as increased commute distances and decreased opportunity for walking and biking have been modelled. When the same home-school route is taken by children walking or commuting by car, the latter experience a lower dose. However, pedestrians can lower their dose by taking an alternative background route or avoiding proximity to traffic queues. A route to school informational intervention, promoting alternative routes with less exposure, showed that most of the participants are willing to change their route.

The influence of school location on commuting mode (active versus travel) as well as on exposure and dose of students has not been studied so far. The study by Wolfe et al. (336) made assumptions on changes in commuting mode and modelled the exposure. As already mentioned in the previous section, more studies with personal monitoring are needed to evaluate the dose in different micro-environments.

### *3.3.4 Design of school and childcare facilities*

#### *Intervention characterization and overview of current interventions*

The design of school and childcare facilities can also contribute to minimize the exposure of children to air pollution while onsite. At EU level no specific policies or regulations are in place to regulate the location and design of schools and childcare facilities in relation to environmental hazards. The aforementioned NICE-recommendation([3]) also cover aspects related to the design of buildings where vulnerable populations reside:

- Site residences away from roadsides;
- Avoid street and building configurations that may enhance pollution;
- Include green infrastructure, keeping in mind that it should be designed to encourage pollution dispersion and removal;
- Include information about how structures such as buildings and other physical barriers will affect the distribution of pollutants

Comparable mitigating measures have also been identified in the review by An et al. (318): locating rooms or places where children often reside away from road traffic, shielding the playground by buildings, walls or by green infrastructure. They also focus on building geometry and orientation which can significantly

([3]) https://www.nice.org.uk/guidance/ng70/chapter/Recommendations

alter natural ventilation patterns, promote pollutant dispersion, and reduce pedestrian exposure to traffic-related pollution (318).

The influence of vegetation on air quality is determined by two different processes. On the one hand, there is the filtering process whereby air pollutants are trapped from the atmosphere. On the other hand, there is the impact of vegetation on the airflow itself whereby the wind speed, wind direction and turbulence of the atmosphere are locally altered, and which, in turn, can affect atmospheric concentrations (340). The review by Abhijith et al. (340) assessed air quality changes due to vegetation in local built environment. They found that in a street-canyon high-level vegetation canopies (trees) led to a deterioration in air quality, while low-level green infrastructures (hedges) improved air quality conditions. For open road conditions, wide, low porosity and tall vegetation (e.g. in the form of green facades with climbing plants) leads to downwind pollutant reductions while gaps and high porosity vegetation could lead to no improvement or even deteriorated air quality (340).

#### *Study search and selection*

A PubMed search was performed on green infrastructure interventions, yielding 0 hits. A Google search yielded different hits. These hits were screened using the methodology by Public Health England (79). A Google search yielded one extra study. This resulted in the inclusion of 3 studies.

#### *Study characteristics and quality assessment*

The effects of green infrastructure specifically in a school environment have been studied in a few individual studies. Tremper et al. (341,342) assessed the efficacy of an ivy (Hedera helix) screen to prevent the transport of vehicle emissions from a nearby road into the playground. The studies focused on $NO_2$ and $PM_{10}$ concentrations and were carried out at two primary schools in London. In the study by Redondo-Bermúdez et al. (343) a green fence of 1.1 m wide and comprising 32 plant taxa, was planted along the playground's edge, next to a stone wall that separates the playground from the adjacent roads. A survey of parents and school staff was carried out to evaluate the perception of the green fence (343).

#### *Changes in activity, emissions, concentrations, exposure and health outcomes and evidence*

Changes in concentration and exposure. Tremper et al. (341,342) measured the difference in concentration between the roadside and playground side of an ivy screen in two London schools. A (matured) ivy screen led to a decrease in pollution concentrations on the playground side by -24% and -38% for $NO_2$ and $PM_{10}$, respectively. During school hours the reductions were even higher amounting to -36% and -41% for $NO_2$ and $PM_{10}$, respectively. The impact of the screen at other spots of the playground at greater distances from the road, has not been assessed (341). In another school similar results were obtained with a reduction of -22% for $NO_2$ (342).

These results are in line with a recent review where Tomson et al. (344) assessed the impact of different green infrastructures for air quality improvement in street canyons. They describe a CFD modelling study demonstrating that green walls (H. helix) reduced in-canyon concentrations of $NO_2$ and $PM_{10}$ by as much as 35% and 50%, respectively (344). Two studies of the review showed that ivy acted as a pollutant sink in high traffic areas and was effective in collecting fine and ultrafine particles (344).

Changes in health outcomes. Redondo-Bermúdez et al. (343) found that the presence of green infrastructure correlates with positive mental wellbeing and enhanced social interactions in playgrounds. It also increases physical activity in children which also results in positive health effects. The presence of green infrastructure also had an impact on attitude and perception, different stakeholders evaluated the presence of green infrastructure in the playground as a positive change in place quality and attractiveness (343).

#### *Considering the setting (if possible)*

Green infrastructure has a limited impact on city-scale air pollution, but it can make a significant difference at the local scale. The magnitude of the effect is dependent on the physical characteristics and type of green infrastructure (e.g. width and height of the green fence, density of plants) as well as place characteristics including built environment type, wind direction and speed, and orientation relative to the source of pollution (343).

#### *Discussion*

Building barriers or green barriers can be used to reduce traffic-related pollution exposure. Local circumstances and space availability determine which type of green infrastructure (e.g. narrow green screen or a wider green wall) can be installed. Few studies measured the effect of green screens and walls on air pollutant concentration on school playgrounds, but the available studies showed significant reductions. Green infrastructures in schoolyards provide multiple social, environmental co-benefits beyond air quality provisioning: cooling, water storage, habitat conservation (343) + EEA NB 2021.

Tremper et al. (342) showed that an ivy screen prevented the transport of pollution from the roadside into the playground, measurements were carried out in the vicinity of the screen. Further research is required to assess the impact of the screen at greater distances from the road. The review by Public Health England (79) stressed the importance for longitudinal studies of green infrastructure interventions on a relatively large scale, together with controlled, long-term, measurements of changes in air concentration of pollutants.

### *3.3.5 Low-emission zones*

#### *Intervention characterization and overview of current interventions*

Many European cities and urban agglomerations have vehicle entry regulations creating low emission zones (LEZ). Entry of the LEZ can depend on vehicle type (e.g. car, van, minibus, bus, coach, etc.) and/or vehicle emission (EURO) category. The instrument hence restricts access to an area for the most polluting vehicles, by either prohibiting them completely or charging an access fee (345). A LEZ introduces a step change in the normal fleet composition, this might place financial burdens on deprived socio-economic groups (346). Over time, the fleet emissions will become similar to those that would have occurred without the LEZ. For further benefits it is necessary to periodically tighten the entry criteria of the LEZ. Other types of traffic intervention include congestion charges, tolling schemes, speed reduction limit, etc. (345).

#### *Study search and selection*

An overview of the selected literature can be consulted in Appendix C: Data extraction. There are only a limited number of studies dealing with the evaluation of LEZ as a tool to improve urban air quality and human health due to various reasons: most LEZs are implemented recently and are dynamic in time with respect to the area covered and the type of restrictions. The literature can be divided in two streams: ex-post evaluation and ex-ante evaluation. Ex-post evaluation studies analyze the effectiveness of a LEZ after a certain period has passed since its implementation. Ex-ante evaluation studies are conducted prior to the implementation of a LEZ and often involve modelling of the accountability chain from change in activity through health impact. Both types of studies have been selected.

In most studies the effect of a LEZ on air quality within the LEZ-region is being assessed for a single LEZ-region. In only four studies (one ex-ante and three ex-post) the health effects of a LEZ with health outcomes in children have been assessed. No meta-analyses or review studies on the effects of LEZ on air quality and health are available, this is because there is a large diversity in the entry restrictions of LEZs and the urban characteristics are determined locally.

#### *Study characteristics and quality assessment*

Table 88 gives an overview of the four ex-post and four ex-ante evaluation studies that have been selected.

## Table 88: Overview of LEZ intervention studies

| Type of study | Study area | Type of LEZ | Activity | Traffic emissions | Air quality inside LEZ | Air quality outside LEZ | Exposure | Health impact | Reference |
|---|---|---|---|---|---|---|---|---|---|
| ex-post | Amsterdam (The Netherlands) | Ban on Euro 0-2 heavy duty vehicles | NA | NA | $NO_2$ -4.5%; Nox -5.9%; $PM_{10}$ -5.8%; EC -12.9% | NA | NA | NA | (347) |
| ex-post | London (UK) | Phase 2 (extra restrictions on light commercial vehicles, 2013-2014) vs phase 1 (restrictions for heavy diesel vehicles, buses and coaches, 2009-2010) | NA | NA | $NO_2$ reduction; $PM_{10}$ no reduction; $PM_{2.5}$ no reduction | NA | NA | pulmonary health children | (348) |
| ex-post | London (UK) | Effect of ULEZ (Ultra Low Emission Zone), Spring 2019 vs Spring 2018 | NA | NA | $NO_2$ reduction; $PM_{10}$ reduction in most sites | $NO_2$ no reduction; $PM_{10}$ no reduction | NA | NA | (349) |
| Ex-post | Berlin, Munich (Germany) | Various types, most stringent: gasoline vehicles Euro 1, Diesel Euro 4 or Euro 3 with diesel particle filters or higher emission standards | NA | NA | $PM_{10}$ reduction; $NO_2$ no reduction | | | | (350) |
| ex-ante | West Yorkshire Zone (UK) | Buses and HGV shift Euro 4 (and lower) to Euro 6, 2016 vs 2012 | Changes in traffic patterns inside and outside LEZ-region | NA | NA | NA | $NO_2$, $PM_{2.5}$ | Mortality and morbidity effects (assessment only inside LEZ) | (351) |
| ex-ante | Coimbra (Portugal) | Personal cars Euro 2 (and lower) entry restriction | Changes in traffic patterns inside and outside LEZ-region | inside LEZ: reduction of $PM_{10}$ and $NO_2$ emissions; city level: increase of traffic emissions | small improvement inside LEZ | NA | NA | NA | (352) |
| ex-ante | Paris (France) | Four hypothetical LEZ scenarios | Changes in traffic patterns inside and outside LEZ-region | NA | $NO_2$ reduction | $NO_2$ reduction | $NO_2$ | Mortality and morbidity effects | (353) |

| Type of study | Study area | Type of LEZ | Activity | Traffic emissions | Air quality inside LEZ | Air quality outside LEZ | Exposure | Health impact | Reference |
|---|---|---|---|---|---|---|---|---|---|
| ex-ante | Malmö (Sweden) | Personal cars shift Euro 5 (and lower) to Euro 6 | No changes in number of vehicles, speed nor type; Changes in emission factors (inside and outside LEZ) | NA | $NO_2$ -13.4% | NA | $NO_2$ | Mortality and morbidity effects (assessment only inside LEZ) | (354) |
| equity of LEZ | Brussels (Belgium), London (UK) | LEZ (Brussels), ULEZ (London, 2021) | NA | NA | $NO_2$ | $NO_2$ | $NO_2$ | accessibility & socio-economic status | (346) |

Four ex-post evaluation studies have been selected:

- Panteliadis et al. (347) assessed the impact of the Amsterdam LEZ on air quality levels for different air pollutants;
- For the LEZ in London, Mudway et al. (348) analysed the effects on air pollution levels inside the LEZ area and assessed the exposure and pulmonary health of children. They performed a cross-sectional study between 2009-2010 (after implementation of phase 1 of the LEZ with restrictions for heavy diesel vehicles, buses and coaches) and 2013-2014 (after implementation of phase 2 of the LEZ with extra restrictions on light commercial vehicles) (348). Bishop and Bornioli (349) assessed air quality levels both inside and outside the ULEZ (Ultra LEZ) that was introduced in 2019;
- Gu et al. (350) validated the effects of LEZ on $PM_{10}$ and $NO_2$ concentrations in two German cities (Berlin and Munich) by utilizing a general additive mixed model to account for confounders in the atmosphere. In addition, the effects of LEZ on elemental carbon (EC) and total carbon (TC) in Berlin were also evaluated. The LEZ effects were estimated after taking into account air pollutant concentrations at a reference site located in the regional background, and adjusting for hour of the week, public holidays, season, and wind direction (350).

Four ex-ante evaluation studies have been selected, they all employed the chain of accountability in a modelling chain starting from a transport model resulting in vehicle kilometers for different vehicle types for different road segments, this is followed by an emission model and an air quality (dispersion and chemistry) model. In some studies, changes in numbers of health events have been estimated by the application of exposure-response functions.

- Lomas et al. (351) performed a modelling analysis for the LEZ in West Yorkshire including the cities of Leeds and Bradford, United Kingdom. On the basis of simulated $NO_2$ and $PM_{2.5}$ exposure levels, the prevented health impact has been estimated for premature mortality, coronary events, cases of childhood asthma as well as low birth weight and preterm birth (351);
- Dias et al. (352) assessed the effectiveness of a hypothetical LEZ in the historic centre of Coimbra, Portugal. Their transport model accounted for a displacement of traffic streams both in and outside the LEZ (352);
- Host et al. (353) modelled the effects of four hypothetical LEZ scenarios for Paris. On the basis of simulated $NO_2$ exposure levels, the prevented health impact has been estimated for premature death, incidence of chronic diseases (ischemic heart disease in adults, asthma in children) as well as low birth weight for newborns (353).
- Flanagan et al. (354) modelled the effects of a hypothetical LEZ scenario for Malmö. On the basis of simulated $NO_2$ exposure levels, the prevented health impact has been estimated for premature death, hospitalization for respiratory diseases, asthma incidence, hypertensive disorders of pregnancy and low birth weight for newborns (354).

Verbeek and Hincks (346) assessed the impact of LEZ on accessibility in urban areas and how this relates to socio-economic patterns for the LEZs in London and Brussels.

It is difficult to draw general conclusions from these studies as the local circumstances (urban situation, type of LEZ) differ greatly. There are, however, some general conclusions one can deduce concerning the changes in activity, emissions, concentrations, exposure, and health outcomes as described below.

***Changes in activity, emissions, concentrations, exposure and health outcomes and evidence***

Changes in activity. In the ex-ante modelling studies, changes in activity and emissions were taken into account in the transport model. In the study by Dias et al. (352) this resulted in extra traffic with more polluting cars outside the LEZ-region. The other ex-ante modelling studies did not report on changes in emissions.

Changes in emission. In the ex-ante modelling studies, changes in activity resulted in changes in emissions. Dias et al. (352) calculated a reduction of $PM_{10}$ and $NO_x$ emissions inside the LEZ coinciding with the historic centre of Coimbra. At the city level an increase in total emissions has been observed (352). The other ex-ante modelling studies did not report on changes in emissions.

Changes in concentration and exposure. Panteliadis et al. (347) estimated the traffic contribution to air pollution in the Amsterdam LEZ by subtracting concentrations measured at an urban background station with measurements in a street frequently used by heavy-duty vehicles. They found significant decreases in traffic-related air pollution concentrations by -4.5% for $NO_2$, -5.9% for $NO_x$, -5.8% for $PM_{10}$ and -7.7% for absorbance and -12.9% for elemental carbon (2 proxies for soot) (347).

After the implementation of the second phase of the London LEZ, concentration of $NO_2$ reduced both at roadside and background locations. However, this was not the case for $PM_{10}$ nor $PM_{2.5}$. The percentage of children living at addresses exceeding the former European limit values of the Directive 2008/50/EC for annual $NO_2$ (40 μg/m³) fell from 99% to 34% (348). No assessment has been made for the new air quality guideline for $NO_2$ of 10 μg/m³ recently recommended by WHO.

After the implementation of the ULEZ in London in 2019 Bishop and Bornioli (349) observed statistically significant reductions of $NO_2$ levels in every site and statistically significant reductions of $PM_{10}$ levels in 3 out of 5 sites located within the ULEZ. At the control sites outside the ULEZ no statistically significant reductions of $NO_2$ and $PM_{10}$ have been observed (349).

The mixed model analysis of the concentrations measured in the LEZ in Berlin, and the LEZ in combination with the heavy-duty vehicle (HDV) transit ban in Munich, indicated a significantly reduction of the $PM_{10}$ concentrations, at both traffic and urban background sites (350). The effects were greater in LEZ stage 3 (gasoline vehicles Euro 1, Diesel Euro 4 or Euro 3 with diesel particle filters or higher emission standards) than in LEZ stages 2 and 1. Moreover, compared with $PM_{10}$, the LEZ was more efficient in reducing EC, a component that is considered more toxic than $PM_{10}$ mass. In contrast, the LEZ had no consistent effect on $NO_2$ levels: no effects were observed in Berlin; in Munich, the combination of the LEZ and the HDV transit ban reduced $NO_2$ in LEZ stage 1, but without further reductions in subsequent stages of the LEZ (350).

The ex-ante modelling studies showed reductions in air pollution concentration levels, however in most cases the air quality levels achieved were not yet compliant with the aforementioned European limit values. In the most stringent LEZ scenario for Paris the maximum level of annual exposure to $NO_2$ from 55 μg/m³ to 42 μg/m³ (353). For the LEZ in Coimbra, the air quality levels showed small improvements, but the average air quality at the city level deteriorated (352). The proposed LEZ in Malmö is estimated to decrease $NO_2$ concentrations by 13.4% (from 15.7 μg/m³ to 2.1 μg/m³ on average), well below the new air quality guideline for $NO_2$ (354).

Verbeek and Hincks (346) deduced for the cities of London and Brussels, after introduction of an (U)LEZ on part of their area, relationships between $NO_2$ concentration levels and household incomes. Air quality levels were determined by combining measurements with air-quality modelling. They found that in the presence of the LEZ lower-income areas are associated with lower exposure levels in London, while in Brussels the lower-income areas have higher exposure levels (346).

Changes in health outcomes. The analysis by Mudway et al. (348) showed that smaller lung volumes in children aged 8-9 was associated with higher annual air pollutant exposures. However they observed no significant reduction in the proportion of children with small lungs after the implementation of the second phase of the London LEZ, despite small improvements in air quality in highly polluted areas (348). Mudway et al. (348) noted that there was no control group and no evidence that the introduction of the LEZ resulted in displacement of more polluting vehicles to regions outside the LEZ (348).

The health impact has been assessed by applying exposure-response functions on simulated concentration levels in three ex-ante studies. Host et al. (353) showed that in the most stringent LEZ scenario for Paris premature mortality decreases with -0,6%, the number of children with low birth weight with -4,9%, the incidence of ischemic heart disease with -1,8% and the incidence of asthma in children with -3,0%. They observed an increase in inequalities (353). The introduction of an LEZ in Malmö showed similar results:

premature mortality decreases with -0.4%, hospitalizations for respiratory disease with -0.4%, asthma incidence with -2.3%, hypertensive disorders of pregnancy with -4.1% and low-birth weight with -0.3% (354). The study by Lomas et al. (351) evaluated the monetary impact of the introduction of the LEZ-area within West Yorkshire: lower exposure to $PM_{2.5}$ lead to reduced premature mortality, coronary events, preterm birth and cases of low birthweight, lower exposure to $NO_2$ lead to lower cases of childhood asthma (351).

Verbeek and Hincks (346) assessed the accessibility of the LEZ in London and Brussels in terms of socio-economic parameters. In both cities lower-income areas are associated with a higher proportion of non-compliant cars that are not allowed to enter the LEZ. In London, people living in lower-income neighbourhoods experience additional travel time by public transport, while in Brussels they have less time by public transport (346).

#### *Considering the setting (if possible)*

The analysis by Verbeek and Hincks (346) shows that local circumstances determine the impact of a LEZ for different socio-economic groups in terms of exposure as well as accessibility. For the hypothetical LEZ in Paris it was shown that extending the LEZ to a wider zone, leads to more equitable spread of benefits over the population (353).

#### *Discussion*

Despite the implementation of LEZ policies in many European cities, no cities have reached the accepted guideline values on ambient air quality set by WHO (345). Ex-post evaluation studies where the effect on concentration levels of $PM_{10}$ and $NO_2$ was measured, yield different results. The ex-ante modelling studies, where standard emission factors were used to estimate vehicle emissions, often indicate greater reductions in modelled air quality levels for $PM_{10}$ and $NO_2$. In only one ex-post study the health impact was measured, showing not statistically signification effects on a respiratory health parameter in children. The ex-ante modelling studies assessed the health impact using exposure-response functions and showed significant reductions in premature mortality and other morbidity outcomes.

The ex-ante modelling studies use standard emission factors instead of considering real driving emission factors, as the latter are higher, it is possible that the emissions are underestimated in their studies. Also, the impact of traffic intensities inside and outside the LEZ-zone and the fleet composition outside the LEZ-zone, is often not measured, and can hence affect the modelling results. The effect of LEZ can have negative effects on health inequalities, depending on how they are implemented.

Longitudinal ex-post studies, possibly including mixed model analysis to correct for confounding factors, are the best means to evaluate the effectiveness of LEZs. In the ex-ante studies, air quality modelling can be improved by considering the use of real driving emission factors, as well as to have more detailed information on fleet composition and traffic flows. The latter data can be obtained by remote sensing technologies, that is often used to ensure policy compliance.

The combination of a LEZ with high quality public transport as well as infrastructure for active transport, might increase benefits.

### *3.3.6 Indoor air quality in schools: measures and awareness campaigns*

#### *Intervention characterization and overview of current interventions*

Several European countries have implemented regulations to ensure adequate indoor air quality. In Flanders, Belgium for example the “Binnenmilieubesluit” is an order by the Flemish government that stipulates guidelines that describe a healthy indoor environment and includes reference and intervention values (355). In 2013 France launched an Indoor Air Quality Action Plan, which includes actions to improve air quality in indoor spaces. By law it was made compulsory to monitor air quality in closed public places that are frequented by sensitive population groups (e.g. day-care centres for children) (356). In Germany a German Committee on Indoor Air Guide Values has been appointed to evaluate indoor air quality (IAQ), set guide values, hygienic guide values and risk-related guide values for health-based assessment (357). $CO_2$ concentrations lower than or equal to 1000 parts per million (ppm) are considered to indicate good

IAQ. Concentrations between 1000 and 1500 ppm are generally considered to indicate moderate and acceptable IAQ (358).

Activities conducted (cleaning, painting, DIY, etc.) in the classroom as well as used products and materials of furniture and equipment are important sources of indoor air pollutants. Minimizing the use of toxic chemicals is an important step in reducing indoor pollutants (359,360). Cleaning practices should be scheduled for after school hours and products should be low-emission cleaning products (2). Cleaning methods should reduce pollutants (wet cleaning vs vacuum cleaning) and should not increase pollutants emission, windows should be opened during and after. In the SEARCH initiative the importance of ventilation after cleaning was demonstrated on asthma and allergy symptoms (361). Wet cleaning is generally considered to eliminate pollutants more efficiently than vacuums. When using a vacuum, it is advised to use a vacuum with high-efficiency particulate air (HEPA) filter (362). Products to wet clean must be carefully considered, since many cleaning products such as bleach can emit pollutants. Lessons that involve the use of products that emit pollutants should be carefully considered (low-emission alternatives and only the required quantity should be used) and scheduled. Direct-exhaust air extraction should be applied when working with toxic chemicals, if this is not possible ventilation should be increased (2,359).

Table 89 and Table 90 give an overview of different aspects of common interventions to improve indoor air quality.

### Table 89: Overview of common interventions to improve IAQ: type of intervention, characterization and further description

| Type | Characterization | Further description | Reference |
|---|---|---|---|
| Natural ventilation | Manual airing of a space by opening windows.<br>• All windows should be fully opened. In case there is no possibility of cross-ventilation, doors should stay closed. If cross-ventilation is possible doors and windows in the neighbouring space (e.g. corridor, …) should also be opened. | • Should be conducted strategically and efficiently.<br>• Measures to optimize natural ventilation: $CO_2$ monitors that visually indicate an increase in $CO_2$ concentration and thus the need for ventilation, create a ventilation schedule.<br>• Ventilation should not be performed during rush hour when the ventilated space is near roads. This could increase indoor air pollutant concentration.<br>• Ventilation should be done after activities that could increase air pollutants concentrations (e.g. cleaning, painting, etc.).<br>• Specifically, ventilation in schools should take place before and after the school day and during breaks, especially during winter.<br>• In polluted areas natural ventilation may increase indoor air pollutants and is therefore often limited. | (359,360,363) |
| Mechanical ventilation | Three types of mechanical ventilation systems:<br>• Type B: mechanical air supply of fresh air and natural exhaust<br>• Type C: natural air supply of fresh air and mechanical exhaust<br>• Type D: mechanical air supply and exhaust. Air is filtered. A heat recovery system can be added, which heats the supplied fresh air to maintain temperature inside. | • Better control of IAQ than natural ventilation.<br>• Rate of ventilation determines air exchange and can be set appropriately to IAQ needs.<br>• Particularly for schools located in polluted areas, where natural ventilation does not necessarily mean an improvement in IAQ, a mechanical ventilation system with filter is beneficial. | (359,360,363–365) |
| Filtration techniques | Filter air pollutants from the air.<br>May be used complementary to ventilation strategies for lowering concentrations of pollutants, especially when no mechanical ventilation system is installed. | • Filter type determines which pollutants are filtered. For example, a high efficiency particulate air (HEPA) filter is most effective on particulate pollutants and not as much on gaseous pollutants.<br>• Portable high-performance air cleaners can be used, but the type needs to be carefully considered since some air cleaners emit harmful by-products.<br>• Should be used in rooms with fresh air supply, since air cleaners circulate the air and do not bring in fresh air.<br>• Example of abatement measure: sorptive boards are gypsum boards that are treated with a sorptive agent. The agent is either a physical sorbent or a chemical agent which both interact in a specific way with volatile organic compounds (VOCs) to eliminate them from the air. | (359,360,363,366,367) |

***Study search and selection***

As described in Section 2.2.5, first a PubMed search was performed which yielded 54 hits. These hits were screened using the methodology by Public Health England (79), which resulted in one study that fit the inclusion criteria. Some common reasons to exclude a study were that the study was non-EU/non-USouth America, the study did not describe a school intervention, or the study merely suggested potential interventions. Additionally, a Google search was performed where one hit of the first ten met the inclusion criteria, meaning the studies discussed interventions to improve IAQ in schools. We were already aware of one study and found one additional study, which were included.

**Table 90: Overview of interventions to improve IAQ in schools: aim and methodology, population and setting**

| Aim of intervention | Population | Setting | Methodology | Measurements | Reference |
|---|---|---|---|---|---|
| 1. To evaluate to efficacy of natural ventilation strategies on $CO_2$ concentration control and compliance of IAQ parameters with the WHO guidelines and Portuguese regulation.<br>2. To evaluate the efficacy of mechanical ventilation and comparison of different mechanical ventilation systems.<br>3. To evaluate the ability of sorptive boards to eliminate formaldehyde.<br>4. To identify and quantify VOC emissions from commonly used products in classrooms.<br>5. To assess the impact of different cleaning practices (wet cleaning vs. vacuum). | 1. One classroom in primary school.<br>2. Three kindergarten classrooms.<br>3. /<br>4. /<br>5. 114 primary schools | 1. Porto, Portugal<br>2. Antwerp, Belgium<br>3. /<br>4. /<br>5. Europe | 1. The case study had a duration of two weeks, during which windows were opened in different arrangements according to a schedule.<br>2. Class 1 had a heat recovery ventilation system; class 2 was aerated through window opening and class 3 was aerated through large sliding doors.<br>3. First test in glass emission test chambers, were active material and non-active equivalent material were exposed to formaldehyde and occurring indoor pollutants (e.g. toluene, benzene, limonene) and compared to each other. Afterwards the sorptive boards were tested in a real-life exposure test chamber in the experimental house MARIA. Experiment took three weeks. During week 1 and 3 the room had no active material and during week 2 sorptive board were installed.<br>4. Five products that are commonly used in classrooms were identified in a classroom walkthrough and emissions tests were performed. These tests were conducted in a emissions test chamber where different European climate conditions were stimulated. Emission tests were also performed inside classrooms.<br>5. Cleaning method, either vacuum or wet cleaning with bleach was determined for the classrooms and the effect of method on IAQ was measured. | 1. $CO_2$ as a proxy for air changes/hour, IAQ parameters.<br>2. $PM_{2.5}$, VOCs and $CO_2$<br>3. Aldehydes and VOCs<br>4. VOCs<br>5. Formaldehyde, pinene and $NO_2$. | (359) |
| To assess different natural ventilation strategies and their effect on $CO_2$ concentration. | 23 primary schools | Switzerland | • Educational and awareness materials were made for the children and a ventilation schedule was set-up, within the rules of the intervention (e.g. ventilation during brakes and before and after the school day, all windows must be opened and hygienic limit of 2000 ppm needs to be complied with).<br>• Teachers received personal and written instructions on how to conduct the intervention accordingly and a standardized lesson was taught to the children.<br>• Baseline concentrations were measured before implementation of the intervention, enabling the comparisons between the concentrations pre and post intervention to evaluate the efficacy of the intervention.<br>• Measurements were taken over the course of four days. | Baseline and during intervention:<br>$CO_2$ | (368) |

| Aim of intervention | Population | Setting | Methodology | Measurements | Reference |
|---|---|---|---|---|---|
| To assess the impact of a mechanical ventilation system retrofit on IAQ and energy consumption. | One primary school. Average classroom occupancy is 28 children. | Cassino, Central Italy. Urban area. | • The classroom was retrofitted with a heat recovery mechanical ventilation system: two mechanical ventilation units, with filters that filter the exhaust air going outside from inside and the fresh air coming inside from outside, were installed on the ceiling.<br>• A $CO_2$ controller, which measures the $CO_2$ concentration and adjusts the fan speed to keep $CO_2$ levels below the pre-set $CO_2$ limit, was connected to the ventilation system.<br>• Pre-retrofit: four different window opening scenarios were tested. Duration: two months.<br>• Post-retrofit: five $CO_2$ based demand-controlled ventilation tests where the pre-set $CO_2$ limit was 1000 ppm, were conducted. Duration: one month. | Pre -and post retrofit:<br>$PM_{10}$ and $CO_2$ | (369) |
| To evaluate the efficacy of an air cleaner intervention on reducing particulate pollutants, the feasibility of implementing such an intervention and its effect on asthma morbidity. | Eighteen elementary classrooms with a total of 25 asthmatic children. | Boston, USA | • Two-arm randomized control trial (RCT).<br>• Commercial air cleaner with HEPA filter.<br>• Intervention group received four HEPA cleaners and control group received four sham cleaners.<br>• Duration: one year.<br>• At the same time the feasibility of an integrated pest management (IPM), which consisted of vacuuming and filling holes and cracks with copper mesh and caulk sealant, was tested. | At baseline and twice during intervention (winter and spring):<br>• $PM_{2.5}$, black carbon (BC) and settled dust allergens.<br>• Asthma symptoms (caregiver questionnaires)<br>• Spirometry measurements: forced expiratory volume in 1 second (FEV1) and peak expiratory flow (PEF) | (366) |

*Changes in activity, emissions, concentrations, exposure and health outcomes and evidence*

**Table 91: Results of the intervention studies to improve IAQ in schools**

| *Changes in activity* | *Changes in emission* | *Changes in concentration and exposure* | *Changes in health outcomes* | *Changes in attitude and perception* | *Reference* |
|---|---|---|---|---|---|
| NR | 1. NR<br>2. NR<br>3. NR<br>4. The selected products were sources of VOC emissions.<br>5. Classes where a vacuum cleaner was used had significantly higher concentrations of formaldehyde, pinene and $NO_2$ compared to classrooms where no vacuum cleaners were used. Similar results were found for formaldehyde and pinene in classroom that were cleaned with a mop with bleach compared to classroom that were not cleaned with mop and bleach. | 1. Natural ventilation according to a specific strategy and schedule was able to keep $CO_2$ below 1500ppm.<br>2. Class 1 had the lowest concentration of $CO_2$, TVOCs and $PM_{2.5}$. Biggest difference between the classes was observed in winter, in summer class 3 (largest aeration surface) had comparable $CO_2$ concentrations to class 1.<br>3. Test chamber experiment: non-active material is uncapable in reducing formaldehyde, active material had an average reduction efficiency of 79%. Real-life chamber experiment confirmed this. Similar effects were observed for acetaldehyde but not for other aldehydes and VOCs | NR | NR | (359) |
| NR | NR | • Significant decrease in median $CO_2$ post-intervention (from 1600 ppm to 1097 ppm) was observed.<br>• Teaching time at $CO_2$ levels between 400-1400 ppm increased to 70% during the intervention vs. 40% in the control group.<br>• Only 10% of teaching time was spent at $CO_2$ levels above 2000 ppm in the intervention vs. 30% in the control. | NR | Standardized lessons were given before the intervention to educate and raise awareness around ventilation, but attitude and perception change was not investigated. | (368) |
| NR | NR | $CO_2$ was reduced in the post-retrofit tests vs. the pre-retrofit tests.<br>Pre-retrofit tests:<br>• Median $CO_2$ = 1756-1085 ppm going from 5 to 20 min/h airing time. | NR | NR | (369) |

| *Changes in activity* | *Changes in emission* | *Changes in concentration and exposure* | *Changes in health outcomes* | *Changes in attitude and perception* | *Reference* |
|---|---|---|---|---|---|
| | | • Air exchange = 0.86 - 2.25 L/s per person for 5 min/h to 20 min/h airing time([4]).<br>• Airborne particle concentration increased with longer airing times and approached the concentration outdoor.<br>• $PM_{10}$ concentrations remained higher indoor than outdoor.<br>Post-retrofit tests:<br>• Summarized median $CO_2$ = 1002 ppm<br>• Air exchange = 4.43 L/s per person[4].<br>• Airborne particle concentration showed a similar trend to the outdoor concentrations; however, the concentration was much lower inside than outside in the post-retrofit tests.<br>• $PM_{10}$ concentrations remained higher indoor than outdoor, however indoor-to-outdoor $PM_{10}$ concentration ratios decreased. | | | |
| NR | NR | First follow-up during intervention:<br>• 49% reduction of $PM_{2.5}$.<br>• 58% reduction of BC.<br>Second follow-up during intervention:<br>• 42% reduction of $PM_{2.5}$.<br>• 55% reduction of BC.<br>• IPM intervention did not affect dust allergen levels | Pre-intervention:<br>• 52% suffered from asthma symptoms in the last two weeks.<br>Six-month follow-up:<br>• 23% reported asthma symptoms.<br>• Reduction in reported asthma symptoms.<br>• Spirometry measurements showed a slight improvement in peak flow.<br>• FEV1 did not significantly change. | NR | (366) |

NR = not reported.

([4]) European EN 15251 standard = 4.88 L/s per person.

***Considering the setting (if possible)***

Natural ventilation can keep $CO_2$ concentrations below 1500 ppm, which is considered acceptable, given that the materials in the classroom have low emissions of pollutants and the allowed density of occupants is respected. Design of the building and construction materials must be considered as well. Location of the school determines the type of ventilation strategy. Outdoor air quality should not exceed guidelines and meteorological conditions need to allow for natural ventilation by way of opening the windows. Natural ventilation should not negatively interfere with the educational activities and performance of the students.

The study by Stabile et al. (369) took place in Cassino, Central Italy. The participating school was located in an urban area. The city is characterized by ambient particle concentration, namely high levels of airborne particles. This needs to be considered in a ventilation strategy (369).

***Discussion***

Only four interventions studies were found to be appropriate for this review, this means that ultimately the evidence that is available on interventions in schools to improve IAQ is quite limited. Additionally, it is difficult for studies to include the large number of factors that need to be considered when implementing an intervention and assessing its efficacy. This makes it difficult to make any conclusion about the impact of interventions in schools on IAQ.

The biggest limitation in the study of Stabile et al. (369) is the small sample size. Only one classroom was investigated. Additionally, emission sources were not taken into account.

The main limitations in the study of Jhun et al. (366) are the small sample size (limiting the interpretation of the studied health outcomes) and the fact that classroom ventilation rates were not measured (entailing that differences in ventilation between the intervention and control classrooms, which could influence the estimates of the efficacy of the air cleaners, were not taken into account). For the IPM intervention, due to limited resources, a partial intervention was implemented in only six classrooms. Additionally, after intervention it was discovered that by chance all the classes selected for the IPM intervention had lower allergen levels than the control classroom. This means that the efficacy of the intervention was impossible to determine (366).

Emission sources are often not considered when implementing an intervention. The first step in improving IAQ is the identification of major air pollutant sources and mitigating them as much as possible before implementing an intervention such as strategic natural ventilation or placing air cleaners.

More pollutants should be investigated; $CO_2$ is often used as a proxy for IAQ, but its behaviour is not representative for all indoor air pollutants. Health outcomes are also rarely investigated as an outcome in an intervention study. This is an important part of assessing the efficacy of an intervention, since IAQ has a big impact on health.

Despite limitations and limited available evidence, one can carefully conclude that the discussed interventions seemed to have had some success and there are many opportunities for future interventions studies. From the results we can conclude that when natural ventilation is the only option for schools to improve IAQ, the most success is achieved when not only guidelines or strategies for the most efficient ventilation are provided but that the teachers and students are also educated about ventilation to raise their awareness.

The added value of ventilation on preventing the spread of COVID 19, has not been discussed in this review. However, most guidelines on preventive measures for COVID 19 include ventilation strategies. Natural ventilation with a considerable air exchange, can reduce the risk of transmission in classrooms. In practice, this is hard to achieve in many classrooms due to their layout. Hence additional measures can be taken, e.g. installation of air filters (HEPA filters can remove SARS-CoV-2) and $CO_2$ sensors to signal the need for ventilation. Mechanical ventilation is better suited to reduce SARS-CoV-2 in the air, although it is best coupled with filters to achieve a greater reduction and avoid cross-infection in different classrooms. Adopting ventilation strategies are therefore not only important for improving IAQ but also preventing the risk of spreading COVID 19 and other similarly transmitted viruses (370).

### 3.3.7 Reduction of secondhand tobacco smoke exposure

#### Intervention characterization and overview of current interventions

The WHO Framework Convention on Tobacco Control (WHO FCTC) is a treaty signed by 182 parties that demands and supports regulatory actions against tobacco use worldwide (371). Many parties used this treaty to establish measures to reduce the use of tobacco in their respective country. In the European Union this led to an issue "Council Recommendation on Smoke Free Environments" by the Council of the European Union. This in turn led to the implementation of smoke-free laws by the member states. All European countries have either a complete or partial ban on smoking in restaurant/bars and indoor workplaces (372). Some countries, like Belgium have a ban on smoking in all closed public spaces and in cars in the presence of children (373).

Interventions to reduce children's exposure to secondhand tobacco smoke (SHS) cover various aspects. Interventions can include training physicians in routinely screening for smoking at doctor visits to increase referral to counselling and quit lines, providing counselling for parents to not smoke in the presence of their child, implementing smoke-free rules in the home to strongly reduce SHS at home or even providing cessation therapy to parents.

The most effective intervention to eliminate SHS exposure is to implement a complete ban on smoking in the entire home by all inhabitants and visitors and all (closed) public spaces. Because addiction is involved, it may be difficult for smokers to quit smoking. A less severe intervention is to make the home smoke-free, which will reduce the exposure but will not fully protect the children. However, this intervention might have more success than forcing parents to quit smoking (374–376). Other interventions include air cleaners to filter harmful pollutants, professional support (e.g. health coach, phone support, counselling), smoking cessation aids (nicotine replacement therapy), biochemical feedback (i.e. reporting child's biomarkers, measures of tobacco smoke pollution), self-help materials, educational materials, etc. An important part in an intervention is the measuring of tobacco smoke pollutants before and after intervention. This can be reported to the parents, increasing the fidelity of the intervention. It also gives an objective measure of the intervention effect particularly when there are measurements pre- and post-intervention and the study has a randomized control group.

For the intervention to be as effective as possible a combination of actions is necessary (375).

Counselling interventions are often a combination of in-person or telephone counselling sessions to support and encourage efforts to reduce SHS at home and/or smoking cessation depending on the objective of the intervention. Participants are often supplied with educational materials additional to counselling. In some interventions, cessation therapy is included on top of counselling. The majority of the interventions listed in Table 92 are counselling interventions.

The standard care provided in the United States of America for tobacco management is 'Ask, Advise, Refer' (AAR). If the clinician/paediatrician/provider screens for tobacco smoke exposure (TSE), they will ask the patient if they smoke or smokers live in the home. This is usually documented in the electronic health/medical record (EHR/EMR). The following steps are then to advise the patient on the dangers of smoking and to advise cessation. In case the patient expressed desire to quit, the provider should refer them to services that assist cessation, e.g. quit lines. Several of the interventions listed in Table 92 are examples of interventions were the EHR was modified to prompt providers to actively screen for tobacco use and to simplify and broaden the subsequent actions. Sometimes this was combined with other intervention types, such as counselling.

**Table 92: Overview of interventions with the aim to reduce SHS exposure of children**

| Name | Intervention characterization | Aim | Reference |
|---|---|---|---|
| Family Rules for Establishing Smoke free homes (FRESH) | • 16 weeks counselling based on a behavioural shaping approach.<br>• Both intervention and control groups received the same material, but the modes and processes were different.<br>• Intervention group received written material that was sent in a span of some weeks, while the control group received the same material in a binder. The intervention group received two in-house counselling session and seven telephone sessions, while the control group were shortly briefed.<br>• During the counselling sessions parents' skills were trained to reduce SHS and support for these efforts was given. Counsellors identified motivators and barriers for the participants during the session, which were used to further personalize the counselling sessions. | To reduce SHS exposure of children. | (377,378) |
| Tobacco control intervention | • 12-week personalized cessation counselling intervention<br>• Intervention group received eight individual in-person/telephone counselling sessions, personalized written self-help materials and eight weeks of nicotine replacement therapy (if they planned on quitting smoking within the next six months).<br>• Control group received educational materials on a healthy lifestyle, self-help materials and contact info to the quit line. | To motivate cessation and reduce smoking in parents. | (379) |
| Head Start Intervention | • 5 motivational interviewing (MI) counselling sessions (in-person or telephone)<br>• Home smoking ban (HSB)<br>• Awareness program to educate the participants on SHS and how to reduce it.<br>• If participants indicated a desire for quitting, this was discussed in the sessions as well. | To reduce SHS exposure of children in their home. | (380) |
| School Based Asthma Therapy trial (SBAT) | • Combined intervention of daily administration of preventive asthma medication and counselling, which focused on educating parents on SHS exposure and how the reduce it and if the parent/caregiver was open to it, cessation counselling was given as well.<br>• One home visit and two telephone sessions at one and three months after the home visit.<br>• The counselling intervention arm had a duration of five months. | To reduce SHS exposure of asthmatic children. | (381) |
| Kids Safe and Smoke free (KiSS) | • Combined intervention of a EHR modification and 12-week personalized behavioural counselling via telephone sessions.<br>• Control group was counselled on attention control with focus on nutrition via telephone sessions.<br>• Both groups received print materials on SHS exposure and tobacco cessation. | To better reduce SHS exposure of children in comparison to the standard care. | (382) |
| Text-messaging cessation intervention | • Five-day text counselling intervention.<br>• Intervention group received 30 personalized texts to counsel and motivate cessation of smoking and control group received texts that covered non-smoking health habits.<br>• Text messages were motivational based on peer network interviews. | To motivate cessation or reduce number of cigarettes smoked per day. | (383) |
| EHR modification intervention | • Combined intervention of an expansion of the normal TSE screening included in the EHR and training of paediatric clinicians on TSE management, which entails counselling and quit referrals.<br>• The modifications made to the EHR made it easier for the clinicians to screen for TSE and in that case refer the patients to counselling or a quit line.<br>• 1-month intervention period. | To improve standard tobacco management in clinic. | (384) |

| Name | Intervention characterization | Aim | Reference |
|---|---|---|---|
| ONE Step intervention | • EHR modification to simplify AAR standard care in clinic.<br>• 16-month intervention period.<br>• The CEASE model is a more extensive tobacco management that uses the three AAR components and 'Assist' and 'Arrange', which requires prescription for cessation therapy. By not including these last two steps, the ONE Step intervention tried to reduce labour and time required by the provider. If a screen is positive and the caregiver is ready to quit, they fill in the ONE Step form, which is then referred to the quit line. | To reduce time and labour efforts in tobacco management. | (385) |
| Take it Right Outside (TiRO) | Television, radio, printed and online advertisement as well as events in shopping centres to inform about SHS exposure and motivate parents to create smoke-free homes. | To reduce SHS exposure of children. | (386) |

***Study search and selection***

As described in Section 2.2.5, first a PubMed search was performed on any interventions with the aim to reduce exposure to SHS of children, which yielded 60 hits. These hits were screened using the methodology by Public Health England (79), which resulted in 14 studies that fit the inclusion criteria. After further screening four additional references were excluded. Additionally, a Google search was conducted where the first ten hits were screened. Of those ten hits, three met the inclusion criteria. Of the 13 selected studies, ten were on counselling interventions. Additionally, we became aware of two systematic reviews, which were included as well.

***Study characteristics and quality assessment***

A systematic review and meta-analysis by Rosen et al. (375) reported on seven studies to determine the effectiveness of interventions to reduce tobacco smoke pollution in homes. All studies measured air nicotine except one which only measured $PM_{2.5}$ and two studies measured child saliva cotinine. Intervention actions included self-help materials, counselling, phone support, NRT, biochemical feedback, air cleaner and tobacco smoke air pollution feedback. Visits ranged from one to ten. All seven studies included a control group. In five studies this control group received some kind of intervention, in one study the controls received self-help materials at the end of the study and in one study the control group received an inactive air cleaner (375).

Champion et al. conducted a systematic review and meta-analysis of intervention studies assessing the impact of parent-based interventions on risk behaviours of adolescents between eight and 16 years old. In this report only the interventions studies that dealt with smoking will be discussed. Nineteen studies implemented interventions targeting smoking. Intervention arms (e.g. type and target population), content and mode in which the intervention was delivered varied between studies (387).

**Table 93: Overview of intervention studies to reduce SHS exposure of children**

| Population | Setting | Methodology | Outcomes | Reference |
|---|---|---|---|---|
| 300 smoking mothers of children younger than 4 years | North and West Philadelphia, Pennsylvania (urban communities) | Two-arm RCT<br>Efficacy of the intervention was determined based on self-reported and biochemical measures. Cotinine is a human biomarker for tobacco exposure and can be used to validate self-reported smoking.<br>Outcomes measures were originally only obtained at baseline and end-of-treatment (EOT). In the follow-up study measures were collected 12 months after EOT.<br>The FRESH intervention specifically targeted underserved mother-children pairs. | Baseline and EOT collection of:<br>• Child urine cotinine<br>• Reported EOT TSE of the mothers<br>• 7-day point-prevalence self-reported cigarettes smoked per day<br>• Saliva cotinine of the mother | (377) |
| | | | 12-month follow-up:<br>• Child urine cotinine<br>• Mother reported TSE<br>• Mother saliva cotinine | (378) |
| 110 smoking parents/caregivers of children between eight and 11 years old | Five counties in an unidentified Southern American State | Two-group RCT.<br>The larger intervention study combined a cessation intervention for smoking parents/caregivers while their children were enrolled in a tobacco prevention program at school. In the larger study 453 parents/caregivers were enrolled. This specific paper only reports on the cessation intervention arm.<br>Efficacy of the intervention was determined based on self-reported and biochemical measures. Cotinine is a human biomarker for tobacco exposure and can be used to validate self-reported smoking. Exhaled CO is a response marker for smoking status.<br>Parents/caregivers were given the opportunity to enrol in year two if they relapsed or refused in year 1.<br>Outcome measures were collected at baseline, EOT and four-year follow-up.<br>The majority of participants was of African American descent and almost half had no high-school degree. | Baseline, EOT and 4-year follow-up:<br>• Self-reported smoking status<br>• Saliva cotinine of parent/caregiver<br>Exclusive measures for participants in intervention group who received NRT at baseline and 3 months:<br>• Exhaled CO | (379) |
| 52 families with children between 6 months and 6 years old | Baltimore City, Maryland (urban communities) | This study was conducted within the setting of a larger intervention study and included a subset of 52 families from the original population of 160 families. The purpose of this addition to the intervention study was to determine the barriers and motivators for smoking cessation and implementing an HSB. During the MI sessions extra questions about what participants experienced as barriers and motivators for implementing an HSB and smoking cessation were asked. Participants of the intervention group were randomly selected for this addition to the intervention study.<br>All families were of African American descent and predominantly low-income. The study area is characterised by high violence and crime rates. | Measures in the larger study:<br>• Household air nicotine levels<br>• Child cotinine<br>• Proportion of families with complete HSB<br>• Quit status<br>Measures of this specific extension:<br>• Barriers for cessation and HSB implementation<br>• Motivators for cessation and HSB implementation. | (380) |

| Population | Setting | Methodology | Outcomes | Reference |
|---|---|---|---|---|
| 140 smoking primary caregivers of children between three and ten years of age | Rochester, New-York (urban communities) | This study assessed one intervention arm of the SBAT intervention, namely the implementation process of a counselling intervention with the goal of reducing SHS exposure at home of children diagnosed with asthma, therefore, it does not report on results of the SBAT intervention in its entirety. 530 children were enrolled in the larger intervention, which spanned three years.<br><br>Efficacy of the intervention was determined based on self-reported and biochemical measures. Cotinine is a human biomarker for tobacco exposure and can be used to validate self-reported smoking. Exhaled CO is a response marker for smoking status. During the second telephone session feedback about evolution of cotinine concentration from the first sample and second sample (collected two months after baseline) was given to the parents. In this article the implementation process and its successes and challenges were reported.<br><br>The majority of participants was of African American descent. | Measures in the larger study at baseline and two-month follow-up:<br>• Child saliva cotinine<br>• Smoking status<br>• Motivation to quit<br><br>Outcomes reported in this article:<br>• Reach of the intervention<br>• Dose delivered<br>• Dose received<br>• Fidelity | (381) |
| 327 parents/caregivers with children younger than 11 years old | Philadelphia, Pennsylvania (urban communities) | Two-arm RCT.<br>The EHR modification was implemented in the paediatric facilities of three large hospital systems.<br>Efficacy of the intervention was determined based on self-reported measures.<br>Clinic level success was determined based on parent/caregiver surveys on AAR conduct by the clinician/provider and quit line referrals.<br>The participants were of low-income families. | Baseline and three-month follow-up:<br>• TSE elimination<br>• Smoke status<br>• Point prevalence abstinence<br>• Prolonged abstinence | (382) |
| 200 smoking adolescents between 14 and 18 years old | Richmond, Virginia (urban communities) | This study is embedded in a larger text-message based MI intervention study. In this secondary part the influence of perceived safety and the density of tobacco outlets within one-half mile of the residence of the adolescents on the impact of the cessation efforts was tested and whether the intervention would abate the effects of perceived safety and outlet density on smoking behaviour. A time-varying effect model was used to do the assessment using data from ecological momentary assessment (EMA) surveys that were sent every Thursday through Sunday each month for 6 months post-intervention. Approximately 90% of the participants were of African American descent | Smoking habits were assessed at baseline, one, three and six-month follow-up. | (383) |
| Parents/caregivers of children | Boston, USA | The intervention was specifically set up in a paediatric care facility to reach people who expose their children (≤ 12 years old) to tobacco smoke. All participating | Three months pre-intervention and three months post-intervention: | (384) |

| Population | Setting | Methodology | Outcomes | Reference |
|---|---|---|---|---|
| younger than 12 years old | | clinicians were given a 15-minute training session on the importance of TSE screening, how to work the modified EHR and how to efficiently conduct a TSE screening.<br>The majority of patients who were served by the clinic were of African American descent. | • Self-evaluation by the clinicians of their TSE screening in clinic.<br>• EHR data (documentation of TSE screening, counselling, and referral).<br>• Quit line referral rates from QuitWorks. | |
| 683 smoking parents/caregivers of children younger than three years | Colorado, USouth America (urban communities) | Satisfaction of the caregivers with the intervention was also collected. Quit line provided data on referrals.<br>Smoking parents/caregivers who filled in the baseline survey were followed up six and 12 months after their visit (n=683).<br>The intervention was implemented in the Child Health Clinic of the Children's Hospital Colorado. Most visitors of the clinic are of low-income. | Baseline, six and 12-month follow-up:<br>• Rate of AAR documentation<br>• Behaviour change of caregivers<br>Six and 12-month follow-up:<br>• Self-reported cessation<br>• Self-reported SHS exposure reduction<br>• Rate of AAR documentation<br>• Behaviour change of caregivers | (385) |
| Children younger than 16 years nationwide | Scotland | Changes in monthly hospital admissions from 2000 through 2018 (TiRO campaign was conducted in 2014) was investigated independently from an effect caused by the smoking ban in public places implemented in 2006 and relative to the underlying trend. | Pre-intervention, one- and four-year follow-up:<br>• Self-reported SHS exposure of children<br>• Hospital admissions of children for respiratory conditions linked to SHS exposure. | (386) |

***Changes in activity, emissions, concentrations, exposure and health outcomes and evidence***

The evidence reported by Champion et al. (387) was not conclusive. All the studies determined efficacy of the intervention via self-reported outcomes. The chance of ever using tobacco at short-term follow-up and using tobacco during the past month at long-term follow-up increased in the intervention group. The interventions had an unintentional iatrogenic effect (387).

No measurements of emission reported in the studies by Rosen et al. and Champion et al. The meta-analysis by Rosen et al. (375) showed a decrease in air nicotine and/or PM at follow-up, although some pollution was still present in the homes. The interventions worked but were not able to entirely reduce pollution. No measurements of health outcomes reported in the studies by Rosen et al. (375) and Champion et al. (387). No measurements of changes in attitude and perception reported in the studies by Rosen et al. (375) and Champion et al. (387).

**Table 94: Results of the interventions to reduce SHS exposure of children**

| Changes in activity | Changes in emission | Changes in concentration and exposure | Changes in health outcomes | Changes in attitude and perception | Reference |
|---|---|---|---|---|---|
| EOT:<br>• Reduction of the number of cigarettes smoked per day.<br>• 19.3% of participants in intervention group reported quitting vs. 3.2% in the control group<br>12-month follow-up:<br>• Participants in the intervention group were still significantly more likely to quit compared to the control | NR | EOT:<br>• Children in the intervention group had lower urine cotinine concentrations vs. the control group.<br>• 13.8% of mothers in the intervention group had bioverified quit status (saliva cotinine concentrations) vs. 1.9% in the control group.<br>12-month follow-up:<br>• Children in the intervention group had lower cotinine concentrations and a significant effect of time showed a decrease in cotinine post-intervention.<br>• 12.3% of mothers in the intervention group had bioverified quit status (saliva cotinine concentrations) vs. 6.1% in the control group.<br>• Mothers in the intervention group reported significant lower exposure to SHS of their children vs. control group. | NR | Through the 12 months after the intervention the positive impact of the intervention was sustained, this could signal a change in attitude and perception. However, this was not measured in the study. | (377,378) |
| EOT:<br>• Self-reported abstinence: 6.5% intervention group vs. 0% control group<br>Four-year follow-up:<br>• Self-reported abstinence: 40.6% intervention group vs. 13.2% control group | NR | EOT:<br>• Significant decrease in parent/caregiver cotinine concentration in intervention group vs. control group where cotinine concentrations increased.<br>Four-year follow-up:<br>• Maintenance of parent/caregiver cotinine concentration in intervention group vs. control group where cotinine concentrations further increased. | NR | Effect on the outcomes of the intervention were sustained through the four-year follow-up, this could signal a sustained change in behaviour and thus perception. This was however not measured in the study. | (379) |
| More families had implemented complete HSBs and increased cessation in intervention group vs. control group. | NR | Household air nicotine concentrations were reduced in intervention group vs. control group. | NR | Factors that are both barriers and motivators:<br>• Social network and asking others to not smoke in the home<br>Illustration: depending on the social network, whether they were supportive or smokers | (380) |

| Changes in activity | Changes in emission | Changes in concentration and exposure | Changes in health outcomes | Changes in attitude and perception | Reference |
|---|---|---|---|---|---|
| | | | | themselves, impacted the way participants viewed this as a barrier or a motivator.<br>• Money and cessation treatment options<br>Illustration: participants who viewed these factors as barriers felt that cessation treatments either didn't work or were too expensive and therefore felt that their smoking habit was less expensive. Other participants felt a sense of confidence in trying to quit in the knowledge that cessation treatment was available, and some felt that the cost of smoking was a way of deterring to continue to smoke.<br>• Weather<br>Illustration: some felt that having to go outside in the cold to smoke would make it difficult to not smoke inside, while some participants actually felt that this was a deterrent to just not smoke.<br>Identified barriers:<br>• Difficulty in finding childcare that did not smoke and not being comfortable with leaving the child alone while going outside to smoke.<br>• Neighbourhood safety and police involvement/harassment was seen as a strong reason not to go outside and participants felt uncomfortable with having to go outside because of it.<br>Identified motivators:<br>• Cleanliness of the home and/or car.<br>• Positive physician support.<br>• Not wanting the child to smoke | |
| NR | NR | NR | NR | • 79% of enrolled participants completed all steps in the intervention.<br>• 80% of participants were satisfied with the counselling they received and reported that it | • (381) |

| Changes in activity | Changes in emission | Changes in concentration and exposure | Changes in health outcomes | Changes in attitude and perception | Reference |
|---|---|---|---|---|---|
| | | | | made them change their smoking behaviour or their efforts to reduce SHS | |
| Three-month follow-up:<br>• 28.2% in the intervention group reported cessation vs 8.2% in the control group. | NR | Three-month follow-up:<br>• 45.8% in the intervention group eliminated SHS exposure vs 29.9% in the control group. | NR | NR | (382) |
| Six-month follow-up:<br>• Adolescents in the intervention group decreased the number of cigarettes smoked per day vs. control group. | NR | NR | NR | Six-month follow-up:<br>• Adolescents in the intervention group increased intention to stop smoking vs. control group.<br><br>The adolescents in the intervention group possibly raised their awareness of the quality of safety as a result of less smoking. Mason et al. determined in a previous study that substance use lowers the ability to gage danger in the environment. This was not verified through any measurements. | (383) |
| Intervention did not impact the number of TSE-screens, it did however greatly increase the number of counselling and referrals to a quit line for positive screens | NR | NR | NR | Most of the clinicians reported that the training before the start of the intervention and the EHR modifications were helpful. A little bit more than half of the clinicians considered themselves to be better at screening and counselling. | (384) |
| Six-month follow-up:<br>• 14% of the participants reported cessation<br>12-month follow-up:<br>• 13% of the participants reported cessation<br>Rate of referrals during the intervention were similar to the Quit line rate in the investigated area. | NR | Six-month follow-up:<br>• 63% of smokers who filled in the surveys reported a reduction in SHS exposure.<br>12-month follow-up:<br>• 70% of smokers who filled in the surveys reported a reduction in SHS exposure. | NR | Parents/caregivers in the intervention group reported that after the intervention they only smoked outside (48% at six-month follow-up and 39% at 12-month follow-up) or smoked less than pre-intervention (34% at six-month follow-up and 36% at 12-month follow-up). | (385) |

| Changes in activity | Changes in emission | Changes in concentration and exposure | Changes in health outcomes | Changes in attitude and perception | Reference |
|---|---|---|---|---|---|
| NR | NR | Parents/caregivers reported a decrease of 50% in the number of children who were exposed to SHS in their home after the intervention. | Four-year follow-up:<br>• Hospital admissions for asthma in children younger than five years was decreased relative to the underlying trend. This was not observed for children between five and 15 years old.<br>• Overall hospital admissions for all children between five and 15 years old did not change relative to the underlying trend following TiRO.<br>• Hospital admissions for respiratory illnesses (bronchiolitis, LRTI and croup) did not show any change following TiRO | NR | (386) |

NR = not reported.

***Considering the setting (if possible)***

All studies except one were set in the United States of America and included a specific target population. The studies by Collins et al. included only low-income participants and the Caldwell et al. (379), Hoehn et al. (380), Blaakman et al. (381), Sharifi et al. (384) and Mason et al. (383) studies included predominantly participants of African American descent. Additionally, most of the studies were set in urban communities. This aspect needs to be considered since it makes generalizability of the results limited. Population wide interventions, such as TiRO are subject to the specific setting of the country in which the intervention is implemented and its population.

***Discussion***

Many of the discussed interventions did not include long-term assessment of the intervention. Additionally, many interventions could not include all relevant effect measures due to limited resources and/or time. Several studies, such as the ones by Sharifi et al. (384) and Bunik et al. (385) did not include a control group. Also, the target population in several studies was very specific which made the generalizability of the results limited. In most interventions self-reported measures were used, which makes the interpretation of the outcomes also limited.

The Turner et al. (386) study, which assessed the population intervention TiRO, has the limitation that it is very difficult to attribute the observed effects to the intervention, because many different factors that are not accounted for could have introduced bias.

These limitations make it difficult to make an over-all conclusion about the success of the interventions discussed in this review, also because the studies are different from each other even those that implemented a similar intervention. Although, we can cautiously conclude that the results reported in the studies seem point to a positive impact of these interventions on SHS exposure of children.

Very few of the discussed interventions measured the impact on health. Considering the facts that SHS exposure has been linked to health problems, more intervention studies should include health outcomes as a measure to assess the intervention. Additionally, many studies did not assess the impact of the intervention on long-term measures and behaviour change, while this is the only way to determine whether an intervention was truly successful and positively affected behaviour. Many studies use self-reported measures, bio verifying this adds more certainty to the results based on self-reporting. Almost no intervention, included the social network of the participants or families. Including participation of the close network and target the intervention to the family could possibly ensure a higher success rate.

The results of the interventions that were discussed and the above-mentioned research gaps show the potential for future interventions that can be implemented and assessed.

### 3.3.8 Smoking bans

#### Intervention characterization and overview of current interventions

**Table 95: Overview of smoking ban interventions**

| Name | Intervention characterization | Aim | Reference |
|---|---|---|---|
| Bavarian smoking ban | Ban on smoking in all closed public spaces since 2008. | To protect non-smokers from SHS exposure and from deterring people, specifically children and adolescents, from becoming smokers. | (388,389) |
| Private car smoking ban | Ban on smoking in private cars in the presence of persons under 18 years old, in England, Wales and Scotland. | To reduce SHS exposure of children. | (390) |

#### Study search and selection

As described in section 2.2.5, first a PubMed search was performed on any interventions with the aim to reduce exposure to SHS of children, which yielded 60 hits. These hits were screened using the methodology by Public Health England (79), which resulted in 14 studies that fit the inclusion criteria. After further screening four additional references were excluded. Additionally, a Google search was conducted where the first ten hits were screened. Of those ten hits, three met the inclusion criteria. Of the 13 selected studies, three were on a smoking ban.

#### Study characteristics and quality assessment

Two studies studied the impact of the Bavarian smoking ban:

- A study conducted by El Sharkawy et al. (389) aimed to investigate the change in SHS exposure to children and prevalence of active smoking in adults after the implementation of the Bavarian smoking ban as well as the impact on children's health. Data was extracted from six of the GME([5]) surveys, two before the ban in 2004 and 2005 and four after in 2008, 2012, 2014 and 2016. Parental smoking in the home with children present was analysed based on all six surveys, parental active smoking was analysed based on the four surveys after the ban, maternal smoking during pregnancy was analysed based on the two surveys before the ban and the surveys from 2014 and 2016. Asthma, bronchitis and neurodermatitis diagnosis and wheezing in the past 12 months was analysed based on the surveys from 2004, 2012, 2014 and 2016 (389).
- Liang et al. (388) also studied the effects of the Bavarian smoking ban on SHS exposure of children in the home and smoking behaviour of the parents. In this study the GME surveys of 2004, 2005, 2008 and 2012 were analysed. Attitude towards a smoking ban and self-imposed smoking rules in the home were also investigated (388).

One of the objectives of both studies was to determine if the smoking ban would cause a displacement of smokers and by consequence SHS exposure to the home (388,389).

In a study by Laverty et al. (390) the effect of the smoking ban in private cars on SHS exposure of children inside cars was investigated using data from a nationwide survey conducted in England, Wales and Scotland. 13,986 children between 11 and 18 years old filled-in the survey and answered questions about their perceived exposure to SHS inside cars (390).

([5]) The GME ('Gesundheits monitoring einheiten'), which is the health monitoring unit of the Bavarian Health and Food Safety Authority, sent surveys every two years starting in 2004 before the ban until 2016. These questionnaires were sent to all parents of 5-6-year-old children during their compulsory school entrance examinations.

***Changes in activity, emissions, concentrations, exposure and health outcomes and evidence***

El Sharkawy et al. (389) observed that the odds that parents never smoked in the presence of their children at home increased significantly from before the ban to the years after the ban. The odds that parents were not actively smoking increased significantly after the ban compared to before the ban. The odds of not smoking during pregnancy also increased over time after the ban (389). Liang et al. (388) did not observe a significant change in the number of parents who ceased smoking after the ban but reported that more families did impose some type of smoking rule in their home after the ban.

The study by Liang et al. (388) investigating the Bavarian smoking ban observed a significant reduction of SHS exposure in the home of the participants post-intervention. They also reported a reduction of SHS in other places, such as restaurants and private cars (388). Laverty et al. (390) reported that the ban on smoking in cars came with a 22% reduction in SHS exposure in cars on top of the underlying trend, which showed that exposure inside cars was already decreasing before the ban. When the analyses were stratified only for girls, children aged 11-14 years and less deprived children a significant reduction in SHS exposure was observed (390).

El Sharkawy et al. (389) reported that the odds of children never having been diagnosed with asthma, bronchitis or neurodermatitis increased significantly after the Bavarian smoking ban. A slight increase in the odds of having four or less wheezing episodes in the past 12 months after the ban was also observed (389).

The Liang et al. (388) study found that parents who believed the smoking ban would cause a displacement of smokers to the home significantly reduced after the implementation of the ban.

***Considering the setting (if possible)***

Population wide interventions, such as smoking bans are very subject to the specific setting of the country in which the intervention is implemented and its population.

***Discussion***

Population wide interventions have the limitation that it is very difficult to attribute the observed effects to the intervention. Many different factors that are not accounted for could have introduced bias. The measures of effectiveness were all self-reported, this makes the interpretation of the results also limited.

In the studies investigating the Bavarian smoking ban it was observed that overtime the response rate of the surveys dropped and that the social make-up of the respondents changed this increased possible bias. It was also assumed that it is very possible that parents/caregivers with a higher education were more likely to fill-out the survey as well as parents/caregivers of children with chronic disease. These are aspects that need to be carefully controlled in future research to reduce the possibility of bias as much as possible. Governments should implement stronger enforcement and in cases similar to the car smoking ban it would be beneficial to extend policies to all cars (instead of just cars with children inside). This on the one hand provides protection to all people riding in cars with smokers and on the other hand make the law much simpler to follow and enforce.

### *3.3.9 Conclusions*

We described the effectiveness of various interventions aiming to minimize the health impact of both outdoor and indoor air pollution and focusing on children. Most outdoor-air interventions target at a reduction of motorized traffic emissions and an increase of active transportation, in order to reduce exposure to hazardous air pollutants during the school – home commute as well as at places where children reside.

The creation of a **clean air zone** around a school can start with anti-idling behavioural campaigns that are proven to be effective in reducing traffic-related emissions in hot spots of drop-off zones often located in the neighbourhood of a school gate and playground. The creation of a school street with a temporary closure of (part of) a street near the school gate, offers benefits for air quality, but also

leads to more active commuting to and from school and possibly respiratory health benefits. The introduction of a school street during a trial period increases the support of the majority of parents and residents.

The **siting of a school and childcare facility** in a low-pollution area, away from busy roads, seems straightforward in achieving health effects, however this affects the **commuting mode** being active or passive. Children can minimize the exposure to air pollutants while walking to school along background routes and by avoiding major intersections. A route to school informational intervention seemed effective as the majority of the participants changed their trajectory to school to less polluted routes.

Concerning the **design of school and childcare facilities**, we focused on the implementation of **green infrastructure** in the environment. An ivy screen is able to reduce pollutant concentrations considerably at least close to the screen. The presence of green infrastructure improves mental wellbeing of pupils and enhances physical activity as well as social interactions in playgrounds.

The implementation of **low-emission zones** in many European cities improved ambient air quality, but not to the level of the ambient air quality guidelines set by WHO. In many ex-ante evaluation modelling studies, the reduction in concentration levels and associated health benefits might be overestimated.

It is often recommended to **combine multiple interventions** as they are likely to act cumulatively. These cumulative gains can build a critical mass: shifting to active travel, improving and creating sustainable environments, and leading to improvement in air quality and health at scale.

**Interventions in schools to improve indoor air quality** show potential, however the number of interventions that can be implemented in existing schools are limited. This is especially the case when it is not an option to renovate the school due to limited resources allocated to schools. Interventions are therefore mostly limited to awareness campaigns and ventilation strategies, which show moderate success and rely strongly on the participation and motivation of the occupants of the classrooms. Particularly ventilation strategies are greatly influenced by the layout of the classrooms and seasonal changes. More traditional interventions (e.g. ventilation and awareness campaigns) are hence effective in improving IAQ in schools, but they are rarely fully sufficient on their own. Co-implementation of various measures could increase the success of the implemented interventions.

A variety of interventions can be implemented both at the individual level as well as at the national level, to **reduce the exposure to tobacco smoke of children**. The success of the interventions targeting the parents/caregivers of children strongly depends on the willingness to implement the intervention, intervention type and mode of delivery. When the intervention team engages the parents/caregivers and provides them with strong support, the motivation often increases. Long-term follow-up of the parents/caregivers increases the fidelity and the chance for a true behaviour change. A combination of different types also shows more success. Co-implementation of various measures has a higher potential of long-term positive effects.

Implementing any type of **smoking bans** at the national level is a legally binding action that the government can take. The protective effect of a smoking ban is dependent on its extensiveness, the highest effectiveness is achieved when smoking bans cover all public spaces and all vehicles. These bans are only as effective as the system that ensures enforcement of the ban. The ban should be as straightforward as possible, unambiguous bans are easiest to enforce and success rates are higher.

# 4 Appendix

## 4.1 Appendix A: Search strategy

The search strings used in the umbrella review are available as Excel spreadsheets (see attached file).

## 4.2 Appendix B: List of identified references

The list of references that have been identified in the literature search are compiled as Zotero files, one of each topic of research (see attached files).

## 4.3 Appendix C: Data extraction

The main features of the literature extracted in the umbrella review are available as Excel spreadsheets (see attached file).

## 4.4 Appendix D: Detailed results on ambient air pollution

### *4.4.1 Mortality and stillbirth and abortion*

#### *$PM_{2.5}$*

Four studies each investigated the association between postneonatal death due to respiratory causes and sudden infant death syndrome and long-term exposure to $PM_{2.5}$ (88). Both effect estimates were not statistically significantly increased. Publication bias could not be excluded. Clear evidence for an association between all-cause and cause-specific mortality and short-term mortality for all ages including children has accumulated according to the two reviews on short-term effects conducted for the WHO guideline process (89,90). Orellano et al (82) reported significant increases for the subgroup of children and adolescents based on 4 studies with short-term exposures to $SO_2$. The review on short-term effects of $PM_{2.5}$, $PM_{10}$, $NO_2$ and ozone did find statistical differences by age, however they did not report effect estimates. The strength of evidence was rated as high for all four pollutants.

Five studies were included on the association between spontaneous abortion and $PM_{2.5}$ (94). Pooled risk estimates yielded a risk ratio (RR) of 1.20 (95%-CI: 1.01-1.40) per 10 µg/m$^3$. There was no indication of publication bias. The evidence according to the assessment with GRADE was categorized as *moderate*. Seven studies investigated the association between still birth and long-term $PM_{2.5}$ (96). Pooled effect estimates for the entire pregnancy were OR 1.103 (1.074-1.131) per 10 µg/m$^3$. Five of these studies also examined trimester-specific effects and found a significantly increased risk of stillbirths for the third trimester with OR 1.094 (1.008-1.180). There was no indication of publication bias. The evidence level was not assessed.

#### *$PM_{10}$*

Nine studies were found on the relationship between post-neonatal all-cause mortality and long-term $PM_{10}$ exposure (88). The pooled effect estimate was significantly increased with OR 1.01 (1.00-1.02) per 10 µg/m$^3$. The risk of post-neonatal death due to respiratory causes was also increased with a pooled effect over four studies with OR 1.13 (1.01-1.27). However, publication bias could not be ruled out. Short- and long-term $PM_{10}$ exposure combined resulted in a pooled estimated of OR 1.08 (1.01-1.17) over eight studies with no indication of publication bias. Regarding sudden infant death syndrome, the risk increased with a pooled OR 1.045 (1.01-1.08) (n=8). The evidence level was not assessed. As for $PM_{2.5}$, evidence for an association between all-cause and cause-specific mortality in all ages including children is high according to the WHO reviews (89,91). However, there are no subgroup analysis for children reported.

Zhu et al. (94) included 5 studies in their meta-analysis and report a pooled RR of 1.09 (95%-CI: 1.02-1.15) per 10 µg/m$^3$. The quality of the evidence was categorized as *moderate*, however, there was an indication of publication bias.

Six studies were combined meta-analytically for stillbirth and long-term $PM_{10}$ (96). Significantly increased pooled effect estimates were calculated neither for the individual pregnancy trimesters nor for the entire pregnancy period. There was no indication of publication bias. The evidence level was not assessed.

Nine studies were found on the relationship between mortality and long-term $PM_{10}$ exposure

***$NO_2$***

The risk of post-neonatal all cause mortality and long-term exposure to $NO_2$ was examined in five studies (88) without indicating a relationship. The authors of the two reviews conducted for the WHO guideline process (89,92) were highly confident in an association between short- and long-term exposure and all-cause and for long-term exposure also cause-specific mortality in all ages including children. However, no subgroup analysis were reported.

Grippo et al. (95) found six studies investigating spontaneous abortion and $NO_2$. One Iranian study reported a significantly positive relationship and a US study a positive but not significantly elevated risk. The other studies failed to support the findings. The results were inconclusive.

Six studies investigated stillbirth and $NO_2$ (96). The summed effect estimates for the third trimester and the whole pregnancy were increased, but not statistically significant. Publication bias was not detected. The evidence level was not assessed.

***Carbon monoxide***

Three studies with conflicting results on spontaneous abortion and carbon monoxide exposure were found. The evidence for an association between spontaneous abortion and carbon monoxide is insufficient.

Stillbirth and carbon monoxide was assessed in six studies without publication bias (96). The summed effect estimate for the whole pregnancy was not increased. However, the estimate for 3rd trimester exposure was marginally but significantly increased with OR 1.009 (1.0001-1.0017) per 10 µg/$m^3$. The evidence level was not assessed.

***Ozone***

Orellano et al (2020) found 48 studies on short-term exposure and all-cause mortality in all ages including children with consistent positive results. The evidence was rated as high. For long-term exposure, the evidence for all-cause mortality and respiratory mortality in all ages including children was low. However, the certainty of evidence for peak ozone exposure was moderate for all-cause mortality in all ages. Effect estimates for children were not reported.

Three of four studies found a statistically significantly increased risk for spontaneous abortion associated with ozone (95). The association is suggestive, however more studies are needed.

Zhang et al. (87) included 7 studies on stillbirth and long-term ozone. The effect estimate summed over 6 studies was significantly increased for the first trimester exposure with OR 1.028 (1.001-1.055) per per 10 µg/$m^3$. Publication bias was not detected. The evidence level was not assessed. Furthermore they found an increased risk for short-term ozone (lag4) based on 4 studies.

***$SO_2$***

Two case-control studies one from Croatia and one from China found significant associations between sulfur dioxide exposure and spontaneous abortion. Due to the small number of studies, no conclusion can be drawn.

Zhang et al. (87) found six studies on stillbirth and $SO_2$ with no indication of publication bias. No significant association were found compelling evidence of an association between air pollution and infant mortality.

### 4.4.2 Birth outcomes

#### Preterm birth

One review (98), one umbrella review (97) and the integrated science assessments of the US EPA for ozone (23) were considered because they are of good quality, searched for multiple databases, conducted a meta-analysis and assed the level of evidence. Additionally we included the US EPA ISA for carbon monoxide from 2010 due to its very detailed assessment of the evidence. The most recent review by Yu et al. (98) included 77 long-term and 13 short-term studies on the association between preterm birth and particulate matter published between 2000 and 2021. The evidence was evaluated with GRADE. Nyadanu et al. (2022) included 36 reviews on birth outcomes and particulate matter, carbon monoxide, ozone, $SO_2$ and $NOx/NO_2$, seven of them on preterm birth and used the JBI critical appraisal tool to assess the evidence. The US EPA ISA on ozone (23) included 22 new studies since the US EPA ISA on ozone from 2010, searched until March 2018, adding up to 29 studies. The ISA on CO found seven studies published from 2000 to 2007. The HEI TRAP review (99)and US EPA ISA on PM (17) were reference to support the overall assessment.

##### $PM_{2.5}$

43 studies were found on the association between preterm birth (less than 37 gestational weeks) and long-term $PM_{2.5}$ (98). The pooled risk estimate was RR 1.084 (95%-CI: 1.055-1.113) per 10 µg/$m^3$. The pooled effect estimates for the exposure in the 2nd and 3rd trimester decreased but was still significantly increased with RR 1.021 (1.001-1.041) and RR 1.020 (95%-CI: 1.008-1.033). Furthermore, for second trimester and entire pregnancy exposure increased estimates were found for moderate (32-37 weeks) and very preterm birth (28-32 weeks). Short-term exposure 2 and 3 days prior to birth was also associated with an increased risk. There was no indication of publication bias. The overall quality of evidence was *moderate*.

##### $PM_{10}$

Yu et al. (98) included 21 studies for $PM_{10}$ for the entire pregnancy exposure period. The pooled effect estimate was increased with a RR of 1.034 (95%-CI: 1.018-1.049). $PM_{10}$ exposure six weeks prior to birth and short-term exposure (two weeks prior to birth and average over 2 days) was also associated with an increased risk for preterm birth. Publication bias was not detected. The quality of evidence across studies on $PM_{10}$ was *moderate*.

##### $NO_2$

Nyadanu et al. (97) found two global meta-analyses and one European meta-analysis. While the evidence for the European meta-analysis based on 4 cohort studies with an OR of 1.14 (95% CI: 0.81-1.64) per 10 ppb for the entire pregnancy with moderate heterogeneity ($I^2$=72%) was classified as "less consistent positive association", the evidence from the two global meta-analyses was "less consistent negative" for 1st trimester exposure and "less consistent positive association" in the 3rd trimester.

##### Carbon monoxide

The association between preterm birth and carbon monoxide during the entire pregnancy or the pregnancy trimesters was assessed as unclear or contradictory in direction by two meta-analysis (97). According to the US EPA ISA there was limited evidence that CO during first and second trimester was associated with PTB.

##### Ozone

Nyadanu et al. (97) included two meta-analyses for the entire pregnancy and the 2nd and 3rd trimester period and three for the first trimester period. The authors found evidence of a less consistent positive association for exposure during pregnancy and the 1st and 2nd trimesters. However, there was no evidence for the third trimester. In line with this, the US EPA has described the relationship between preterm births and 1st and 2nd trimester ozone exposure as "fairly consistent". Based on the well-designed studies, the evidence of an association was considered "suggestive".

#### Overall

Overall, the included reviews found well-conducted studies showing an association between preterm birth and particulate matter and ozone. Even if there are still contrary results and a lack of co-pollutant models, there was little detected publication bias. The epidemiologic evidence is still limited, but taking evidence from toxicological studies into account, the relationship is *suggestive* according to the US EPA ISA on ozone (23) and PM (17). However, a relationship between preterm birth and other pollutants is inconclusive and according to the US EPA ISA on PM the biological mechanisms playing a role are still uncertain. This is in line with the WHO reporting a growing evidence between preterm birth and air pollution, especially for PM.

#### *Birth Weight*

Two reviews (100,101) and one umbrella review (97) were included, as well as the integrated science assessment of the US EPA for ozone. Ghosh et al. (100) investigated the association between birth weight and $PM_{2.5}$ and found 44 studies published between 2005 and 2020. Yang et al. (101) investigated effects of PAHs and included 12 studies published between 1998-2017. Both reviews conducted a meta-analysis and assessed the level of evidence. Nyadanu et al. (97) included 36 reviews on birth outcomes and particulate matter, carbon monoxide, ozone, $SO_2$ and $NOx/NO_2$, seven of them on birth weight and used the JBI critical appraisal tool to assess the evidence. The US EPA ISA on ozone from 2020 (23) included 7 new studies since the US EPA ISA on ozone from 2010, searched until march 2018, adding up to 19 studies. Since there were no recent reviews on benzene the review by Protano et al. (102) from 2012 was added to the analysis as well. They found only 3 studies published between 2003 and 2011. Additionally for TRAP we also included the HEI report (99) that examined 18 studies. As supporting evidence we also included the US EPA ISAs on PM (17) and $NO_2$ (25).

#### $PM_{2.5}$

Ghosh et al (100) included 44 studies in their meta-analysis. The pooled estimate showed a 22 grams (95%-CI: 12-32) reduction in birth weight per 10 µg/m$^3$. Restricting to 13 studies that included all births (term and preterm births) increased the estimate to 35 g (95%-CI: 15-55) per 10 µg/m$^3$. There was no indication of publication bias, however, the between-study heterogeneity ($I^2$) was high (>99%). The authors graded the evidence as *strong*. Nyadanu et al. (97) included six meta-analysis with significant estimates between 15 and 28 grams weight reduction and concluded that the association is more *positive consistent*. Consistently, the HEI report observed a significantly decreased term birth weight associated with traffic-related $PM_{2.5}$ based on six studies.

#### $PM_{10}$

Three meta-analysis showed a less consistent positive associations with $PM_{10}$ exposure. The largest pooled reduction in birth weight was reported with 10 grams (7-14) per 10 µg/m$^3$ (97).

#### $NO_2$

Nyadanu et al. (97) included one global and one European review. Since the European review reported a not significantly decreased lower birth weight associated with $NO_2$ during the entire pregnancy but the global one did, the association was assessed as less consistent positive. The exposure in the second trimester even showed an unclear or contradictory direction.

#### Carbon monoxide

Nyadanu et al. (97) found one meta-analysis based on four cohort studies. The overall evidence was rated as unclear or contradictory direction.

#### $SO_2$

Nyadanu et al. (97) found one review reporting unclear or contradictory directions of the association between birth weight and exposure to $SO_2$.

#### Ozone

The association was less consistent positive for the exposure in the second trimester and unclear for the other pregnancy periods according to one meta-analysis (97). The US EPA (23) also found positive associations, but found variability in timing of exposure and the magnitude of effect estimates varied. However, animal toxicological evidence (rodents) showed decreased birth weight in association with ozone exposure, which is why they assessed the epidemiologic evidence overall as suggestive.

#### PAHs

A one ln unit (ng/m3) increase of airborne PAHs was associated with reduced birth weight based on 4 studies (101). The heterogeneity $I^2$ was high (87.17%). The quality of the individual studies was moderate. Furthermore, the review also reported no association with PAH-DNA adducts in cord blood or 1-hydroxy pyrene in maternal urine.

#### Benzene

One out of three studies found significant decreased birthweight associated with BTEX, while birthweight in another study was insignificantly decreased and one study observed no relationship with benzene (102).

#### Overall

Overall, the most consistent association was found between continuous birth weight and $PM_{2.5}$ without indication of publication bias. However, heterogeneity was high. Without the inclusion of other studies, such as toxicological studies with animals, the evidence for a relationship between birth weight and exposure to $PM_{10}$, $NO_2$ and Ozone was less consistent positive. However, when possible biological pathways are included, the evidence might be *suggestive*.

### *Small for gestational age*

Two reviews with a meta-analysis (99,103) and one umbrella review were included. Pun et al. (103) found 49 studies on ambient particulate matter and 17 studies on indoor air pollution and cooking published between 1990-2020. Risk of bias (RoB) and level of evidence was not assessed. In contrast, the HEI report (99) on traffic-related air pollution (TRAP) conducted a thorough RoB according to OHAT and included 25 studies on small for gestational age. Nyadanu et al. (97) included 36 reviews on birth outcomes and air pollution, two of them on SGA and $PM_{2.5}$. JBI critical appraisal tool was used to assess the evidence.

#### $PM_{2.5}$

Pun et al. (103) included 18 studies for the entire pregnancy exposure, 11 for the first and 10 each for the second and third trimester. The pooled risk for SGA was increased with OR 1.08 (95%-CI: 1.03-1.13) for the entire pregnancy and with OR 1.04 (1.02-1.06) and OR 1.05 (1.00-1.09) for the second and third trimester period per 10 µg/$m^3$. However, heterogeneity was high ($I^2$=78-92%). The effect estimate for the traffic-related $PM_{2.5}$ was comparable to OR 1.09 (95%-CI: 1.04-1.14) per 5 µg/$m^3$ for the entire pregnancy period based on four studies (99) with minimal heterogeneity ($I^2$=0%). The HEI panel assessed the evidence for $PM_{2.5}$ as low due to the modest amount of large birth cohort studies. Based on two meta-analysis, Nyadanu et al. (97) rated the association as *less consistent positive* for the entire pregnancy and the second and third trimester and as unclear for the first trimester.

#### $PM_{10}$

The pooled effect estimate for the entire pregnancy based on 12 studies was OR 1.03 (1.00-1.05) per 10 µg/$m^3$ (103). Exposure in the first trimester also showed increased risk with OR 1.01 (1.00-1.03) based on 11 studies. Heterogeneity was high ($I^2$=85-87%). An increased risk was also found for traffic-related $PM_{10}$ based on 4 birth cohorts in the HEI report (OR 1.08 (1.01-1.14) per 10 µg/$m^3$) with less heterogeneity between studies ($I^2$=11%). According to one study (391) the dose-response function before and after an inflection point of 27 µg/$m^3$ seemed to be linear. The assessment of confidence was *moderate*.

#### $NO_2$

11 studies were included in the meta-analysis in the HEI report (99). There was no increase in the risk of SGA (OR 1.00 (95%-CI:0.96-1.04) per 10 µg/m$^3$)) for traffic-related $NO_2$ exposure in the entire pregnancy period. For $NO_2$ there were sufficient studies to evaluate publication bias, which was not found using Egger test. The evidence was assessed as *moderate*.

#### EC

Based on 3 birth cohorts, the HEI report (99) found no association between SGA and EC (OR 1.02 (95%-CI: 0.92-1.14)). The body of evidence was considered as *very low*.

#### Overall

Overall, SGA is less frequently studied than preterm birth or low birth weight. There is some evidence that an increased risk might be associated with SGA. However, the number of well-designed studies is low and the heterogeneity between studies high. The HEI report (99) considered the evidence for traffic-related $PM_{2.5}$ as *low* and for $PM_{10}$ as *moderate*. Taking into account the narrative assessment, the overall evidence for TRAP was assessed as *moderate*.

### *(Term) low birth weight*

One review (100), the HEI TRAP report (99) and one umbrella review (97) were included. Ghosh et al. (100) investigated the association between low birth weight and $PM_{2.5}$ and found 40 studies published between 2005 and 2020. Nine studies included all births not only term births. The association between term low birth weight and traffic-related $PM_{2.5}$, $PM_{10}$, $NO_2$, NOx and EC was investigated in the HEI report (99). They found 25 studies published between 2003-2019. Nyadanu et al. (97) included 36 reviews on birth outcomes and particulate matter, carbon monoxide, ozone, $SO_2$ and NOx/$NO_2$, seven of them on low birth weight. All articles conducted a meta-analysis and assessed the level of evidence.

#### $PM_{2.5}$

Ghosh et al. (100) reported a pooled (n=40) estimate for LBW with 11% (95%-CI: 7-16) increased risk per 10 µg/m$^3$ for the entire pregnancy period. The heterogeneity was high ($I^2$=95%) and there was an indication of publication bias. Nevertheless, the authors graded the evidence as *strong*. 3 out of 7 meta-analysis found a significantly increased risk for $PM_{2.5}$ exposure during the entire pregnancy period (97) and the other four studies positive associations. Therefore, the authors assessed the association between LBW and $PM_{2.5}$ in the entire pregnancy period and each trimester as less consistent positive. The HEI report (99) found *moderate* evidence for term LBW based on seven studies for traffic-related $PM_{2.5}$. The pooled effect estimate was RR 1.11 (95%-CI: 1.03-1.20) per 5 µg/m$^3$ during the entire pregnancy period with high heterogeneity ($I^2$=84%). Publication bias could not be assessed due to the number of studies (n<10). Three studies demonstrated a monotonic exposure-response function.

#### $PM_{10}$

Four meta-analysis were included in the umbrella review (97) with positive effect estimates for LBW. Two of them were statistically significant for the entire pregnancy period. The overall evidence was graded as a *less consistent positive* association for the entire pregnancy period and the first and second trimester, but unclear or contradictory for the third trimester period. The HEI report (99) found 3 studies on term LBW, with one significantly increased estimate and two positive estimates including the null. The pooled effect estimate was RR 1.14 (95%-CI: 0.95-1.38) per 10 µg/m$^3$ with minimal heterogeneity ($I^2$=0%). The evidence was rated as *low*.

#### Carbon monoxide

Two meta-analysis based on six and eight studies were included (97). Both reported a pooled increased risk of 1% (95%-CI: 0-1) per 100 ppb CO for the entire pregnancy period with low to moderate heterogeneity. There was also evidence of a less consistent positive association for the second trimester exposure period. The HEI report (99) included 3 studies for the association between term

LBW and traffic-related CO with a pooled effect estimate of RR 1.06 (95%-CI: 0.67-1.68) per 1 mg/m3 and moderate heterogeneity ($I^2$=52%). The body of evidence was rated as *very low*.

#### $NO_2$

Nyadanu et al. (97) included two meta-analysis. Both reported positive significant associations for the entire pregnancy period. The larger pooled effect estimate was 1.03 (95%-CI: 1.01-1.05) per 10 ppb based on 23 cohort studies. However, heterogeneity was high ($I^2$=90%). The association was assessed as *less consistent positive* for the entire pregnancy period and the first and second trimester and *unclear or contradictory for the third trimester* period. The HEI report (99) included 12 studies. The meta-analysis showed no association between traffic-related $NO_2$ exposure and term LBW. Seven studies evaluated the exposure-response function and four of them found a monotonic function for term low birth weight and traffic-related $NO_2$. The overall evidence was assessed as *high*.

#### NOx

Five birth cohort studies investigated the association between TLBW and traffic-related NOx exposure (99). The pooled effect estimate was RR 1.02 (95%-CI: 1.01-1.02) for the entire pregnancy and RR 1.01 (95%-CI: 1.01-1.02) per 20 µg/$m^3$ for the third trimester. There was no heterogeneity between studies. The evidence was rated as *moderate*.

#### Ozone

The results of two meta-analysis reported by Nyadanu et al. (97) indicated unclear evidence for an association between LBW and exposure to ozone in the entire pregnancy period or the first and second trimester. However, there was a *less consistent positive association* for the exposure in the third trimester.

#### EC

The pooled estimate from 5 studies (99) showed no increase in risk for traffic-related exposure in the entire pregnancy or the first trimester. However, there were suggestive associations for the second and third trimester with RR 1.02 (95%-CI: 1.01-1.04) and RR 1.03 (95%-CI:1.03-1.04) per 1 µg/$m^3$. There was one large study with a lot of weight (87%). The evidence was rated as *moderate*.

#### $SO_2$

Nyadanu et al. (97) included two meta-analysis. Both reviews reported significant increases in risk with pooled effect estimates RR 1.12 (95%-CI: 1.02-1.24) and RR 1.06 (1.04-1.10) per 10 ppb for the entire pregnancy. While the heterogeneity in the study with the higher estimate was high, there was no heterogeneity in the other meta-analysis. Nyadanu et al. (97) concluded, that the association between LBW and $SO_2$ is *more consistent positive*.

#### Overall

Overall, most evidence for an association with term low birth weight was found for $SO_2$, as well as for traffic-related $PM_{2.5}$, NOx and EC. There is some evidence for a monotonic dose-response function.

#### *Intrauterine growth restriction*

One review by Fu et al. (104) was included. They investigated the association between intrauterine growth restriction measured by ultrasound and anthropometric indicators at birth such as head circumference and exposure to $PM_{10}$, $PM_{2.5}$, $NO_2$, NOx, $SO_2$, carbon monoxide and ozone. 15 studies published between 2007 and 2017 were included. Meta-analysis and RoB assessment was conducted for $PM_{2.5}$, $PM_{10}$ and $NO_2$. Body of evidence was evaluated with GRADE.

#### $PM_{2.5}$

3 studies were pooled the association between head circumference at birth and the exposure for the entire pregnancy period (104). The head circumference decreased significantly by 0.3 cm (95%-CI: 0.1-0.49) per 10 µg/$m^3$. Heterogeneity was moderate to high ($I^2$=73.48%) with no indication of publication bias. The authors rated the evidence as *moderate*.

#### $PM_{10}$

3 studies each were included for head circumference and $PM_{10}$ exposure during the entire pregnancy and the third trimester (104). The pooled effect estimates were not statistically significant and the evidence for the association was rated as *low*.

#### $NO_2$

4 studies were included in the meta-analysis for birth length. The length at birth decreased significantly by 0.03 cm (95%-CI: 0.02-0.05) per 10 µg/m$^3$ (104). There was no heterogeneity between studies. The evidence for the association was *low*. 8 studies investigated the association between head circumference and the entire pregnancy period and 3 for the third trimester. Neither of the two relationships were associated with each other. The evidence was assess as *very low*.

#### Overall

Overall, exposure to higher $NO_2$ and $PM_{2.5}$ levels might reduce head circumference and birth length. However, the effects of air pollutants on intrauterine growth remain inconclusive due to the general low number of studies and the rather low methodological quality of studies.

### *Malformations*

Two reviews (106,107) and the US EPA ISA on ozone (23) and carbon monoxide (32) for congenital heart diseases, two for orofacial defects and other anomalies (Ravindra et al. 2021, Rao et al. 2016) and two reviews for hypospadias (109,110) were included. Xing et al. (109) investigated the association between hypospadias and the exposure to particulate matter, $NO_2$, ozone, $SO_2$ and carbon monoxide. They found 16 studies published between 1998-2020 and conducted a RoB assessment with OHAT and a meta-analysis. We also included Lin et al. (110) since they report other results based on the same studies in the meta-analysis. Evidence was not assessed in both studies. Ma et al. (106) investigated the association between congenital heart disease and particulate matter, $NO_2$, $SO_2$, carbon monoxide and ozone. They found 24 studies published between 2002 and 2019. A meta-analysis was conducted, but the quality of the body of evidence was not examined. Ravindra et al. (107) examined various congenital anomalies, including congenital heart diseases and included 26 studies published between 2009 and 2018. They also did a meta-analysis and used ROBINS-E to evaluate risk of bias and the evidence. Furthermore the US EPA ISA for CO (32) included 5 studies and the ISA for ozone (23) 12 studies since the last report 2013. Rao et al. (108) investigated the association between orofacial clefts and particulate matter, $SO_2$, $NO_2$, carbon monoxide and ozone in 8 studies published between 2000 and 2012. A meta-analysis was conducted and risk of bias was assessed, but not the level of evidence. The newer review by Ravindra et al. (107) additionally examined the relationship between AP and multiple congenital anomalies (orofacial clefts, limb defects, nervous system anomalies and other congenital anomalies).

#### $PM_{2.5}$

Xing et al. (109) and Lin et al (110) report significant increases in the risk of hypospadias and first trimester exposure based on five studies. Xing et al. (109) used 10 µg/m$^3$ increments, while Lin et al. (110) used IQR for pooling. The pooled effect estimates were OR 1.34 (95%-CI: 1.06-1.68) per 10 µg/m$^3$ and RR 1.17 (1.00-1.36) per IQR increase with moderate heterogeneity between studies (I2=54.7% and 56.8%). Xing et al. (109) did not find publication bias, whereas Lin et al. (110) conducted trim and fill method due to significant publication bias detected with Egger test. The pooled risk estimate diminished to RR 1.03 (0.89-1.19). In the main analysis, Ma et al. (106) found no significant association between $PM_{2.5}$ and congenital heart disease pooled over 9 studies. However, in a subgroup of studies from developing countries, the odds for ventricular septal defect were increased with OR 1.208 (95%-CI: 1.080-1.337). However, the increment of this association was not reported. There was no other significant association with other types of congenital heart diseases. Ravindra et al. (107) pooled 3 studies for the risk of pulmonary valve stenosis and Tetralogy of Fallot with high heterogeneity ($I^2$= 98.4% and 97.6%). The risk estimates were 1.42 (95%-CI: 1.36-1.48) and 1.52 (1.44-1.60) per 5 µg/m$^3$.

Furthermore, Ravindra et al. (107) pooled 4 studies for the risk of limb defects and 3 studies for the risk of neural tube defect and found a significantly decreased risk estimates (OR 0.76 (95%-CI: 0.72-0.80) and OR 0.87 (0.75-0.98) per 5 µg/m$^3$) with high heterogeneity. The evidence was rated as *low and very low*. Finally, they examined the association between the risk of spina bifida and $PM_{2.5}$ in three studies, but found no association.

#### $PM_{10}$

Xing et al. (109) included seven, Lin et al. (110) six studies on hypospadias. While some studies found positive, some negative associations, none of the associations was statistically significant. Meta-analysis was not conducted. Congenital heart defects were not related to $PM_{10}$ in the overall analysis (n=13) (106). In a subgroup of studies, where the exposure time was within 3-8 weeks, there was a positive association with ventricular septal defect (OR 1.057 (95%-CI: 1.005-1.109). However, the increment of this association was not reported. Rao et al. (108) found inconsistent results on the risk for orofacial cleft (both cleft lip with or without palate). There was no relationship in the meta-analysis based on five studies. In a newer review by Ravindra et al. (107) two additional studies were included in the meta-analysis, but 4 other publications were missing. The pooled estimate (n=3) was significantly decreased with OR 0.87 (95%-CI: 0.79-0.93) per 10 µg/m$^3$. Additionally, they found a decreased risk for limb defects based on four studies with OR 0.83 (95%-CI: 0.80-0.86) per 10 µg/m$^3$ with high heterogeneity.

#### NOx

Five studies investigated the risk of hypospadias and NOx (109). Although exposures 3 months post conception were mainly positively associated with hypospadias, none of them were statistically significant. One study found a statistically significant increased risk for the exposure to NOx and $NO_2$ during the periconceptional period. None of the different types of congenital heart diseases were related with $NO_2$ (n=12) (106). Ravindra et al. (107) found a pooled (n=3) increased risk for pulmonary valve stenosis associated with $NO_2$ with OR 1.74 (95%-CI: 1.68-1.81) per 10 ppb. Rao et al. (108) found a significantly decreased risk for cleft palate only based on 4 studies with OR 0.84 (95%-CI: 0.71-1) (increment not reported).

#### Carbon monoxide

In the preliminary analysis, the risk for atrial septal defects decreased significantly based on seven studies (106) (effect estimates not reported). No further associations were found in the subgroup analysis. In contrast, the US EPA assessment from 2010 (32) concluded, that there is *some evidence* that the risk of congenital anomalies, especially heart defects are associated with carbon monoxide exposure during pregnancy. Rao et al. (108) found a significantly decreased risk for cleft palate only based on 4 studies with a pooled OR 0.88 (95%-CI: 0.78-0.99) (increment not reported).

#### $SO_2$

Ma et al (2021) included 12 studies on the risk of vascular septal defects, which was significantly decreased (EE not reported). Accordingly, based on 3 studies, the risk for atrium septal defects was significantly decreased with OR 0.87 (95%-CI: 0.86-0.87) per 1 µg/m$^3$ (107), but the results from the individual studies were inconsistent and the evidence therefore rated as *low*. The pooled risk for orofacial clefts was not associated with $SO_2$ according to six individual studies (108).

#### Ozone

Xing et al. (109) included 4 studies and 3 of them in the meta-analysis. With moderate heterogeneity ($I^2$=53.5%) the exposure in the first trimester was not associated with hypospadias risk (OR 1.03 (95%-CI: 0.96-1.11) per 5 ppb ozone). Furthermore, publication bias was discovered with Egger's test. In the preliminary analysis, ozone was not associated with congenital heart defects (106). However, in the subgroup of studies from developing countries, the pooled risk was OR 1.205 (95%-CI: 1.101-1.310) (increment not reported). According to the evaluation of the US EPA (23), findings on birth defects and

ozone are inconsistent. Rao et al. (108) pooled 4 studies examining the association between the risk of cleft lip with or without palate and ozone. They found a significantly increased risk of OR 1.08 (1.01-1.16).

#### Overall

Overall, very few studies have examined the association between hypospadias and air pollution. There is *insufficient evidence* to determine a relationship. Similar to hypospadias, there is *very limited evidence* for a relationship between air pollution and orofacial clefts. The most suggestive evidence was found for ozone. However, there is no supporting evidence from experimental animal studies according to the US EPA ISA for ozone (23). The risk of limb and neurological defects have rarely been studied in epidemiological studies. There is some evidence that maternal exposure to air pollution is associated with an increased risk of congenital heart diseases, which is partly supported by some animal toxicological studies. However, there are contradictory results and no consistent linear or dose-response relationships between malformations and any air pollutant are reported. Further studies are needed to clarify such associations. The evidence for a relationship between malformations and air pollution altogether is low. Additionally, none of the UN-reports has reported on this outcome.

### *4.4.3 Respiratory effects*

#### *Infections*

#### $PM_{10}$ / $PM_{2.5}$

Long-term exposure to $PM_{2.5}$ was significantly associated with ALRI in Mehta et al. (111) with RR 1.12 (95%-CI: 1.03, 1.30) 10 µg $PM_{2.5}$/m3 based on 4 studies. Publication bias was not assessed. Nhung et al. (113) also reported significantly increased risks for pneumonia with short-term exposure to $PM_{2.5}$ and $PM_{10}$, e.g. 1.018 (95%-CI: 1.005, 1.031) with low heterogeneity based on 13 estimates. Risk of bias was not assessed. Long-term exposure to both PM metrics showed a non-significantly elevated risks. The rigorous review by King et al. (114) studying bronchiolitis found only eight studies with PM and concludes that the studies on $PM_{2.5}$ indicate no increased risk for hospitalization with short-term exposure but possibly with long-term exposure based on moderate quality of the studies. Evidence for $PM_{10}$ was of *low quality* and acute and lifetime effects seem inconclusive. Publication bias was not assessed due to low number of studies. Lee et al. (115) also found significantly increased risks of **otitis media** with short-term PM exposure, with more consistent associations with $PM_{2.5}$ exposure as compared to $PM_{10}$ with no indication of publication bias. Whereas another review found most consistent evidence with $NO_2$ and inconsistent association with other pollutants (116). Ziou et al. (117) found *moderate* evidence for the short-term association of $PM_{2.5}$ and $PM_{10}$ with upper respiratory infections with significant publication bias. However, after trim-and-fill results remained unchanged. The US EPA ISA (17) saw *consistent* evidence for an association of overall respiratory infections with short-term $PM_{2.5}$ exposure but mixed results for categories of infections such as pneumonia. There was no clear evidence for long-term effects with $PM_{2.5}$.

#### $NO_2$

The 2016 US EPA ISA (25) found not entirely consistent results for acute effects of $NO_2$ on respiratory infections and some evidence for long-term effects in school children but not infants. King et al (114) found a possible long-term effect on **bronchiolitis hospital admissions** with moderate quality of evidence and unclear effects of short-term exposure, whereas Nhung et al. (113) reported significant increases in **pneumonia** risk with short-term exposure to $NO_2$. Risk of bias was not assessed. Bowatte et al. (116) found the most consistent association for otitis media with $NO_2$ exposure compared to other pollutants with low indication of publication bias. Finally, the HEI (99) found moderate to high evidence for an association of ALRI with long-term exposure to TRAP partly based on significantly increased risk with long-term exposure to $NO_2$ with RR 1.09 (95%-CI: 1.03, 1.16) per 10-µg/m3.

#### Ozone

The US EPA ISA (23) found consistent evidence of an association between short-term ozone exposure and ED visits for a variety of respiratory infection endpoints. Nhung et al. (113) reported significant increases in pneumonia risk with short-term exposure to ozone RR 1.02 (95%-CI: 1.01, 1.03) per 10 ppb ozone with high heterogeneity of studies. Risk of bias was not assessed. Only a few studies were listed in Bowatte et al. (116) regarding otitis media risk. Results on effects of long-term exposure are counter-intuitive with the US EPA (23) and King et al. (114) reporting inverse associations with respiratory infections and bronchiolitis risks. However, this is based on a very limited number of studies and low quality regarding the bronchiolitis studies.

#### $SO_2$

The 2017 US EPA ISA (24) saw some, but not entirely consistent evidence supporting an association between ambient $SO_2$ concentrations and respiratory infection. Short-term associations seem more consistent than long-term associations. This is supported by the significantly increased pneumonia risk with short-term $SO_2$ exposure in Nhung et al. (113) RR 1.029 (95%-CI: 1.004, 1.053) per 10 ppb with medium heterogeneity. Risk of bias was not assessed. As well as the mentions in the bronchiolitis review finding some evidence for acute, sub-chronic, and lifetime exposure, however with low quality of studies (114) and a few studies on otitis media risk listed in the review by Bowatte et al. (116).

#### EC / Traffic

The HEI (99) found moderate to high evidence for an association of ALRI with long-term exposure to TRAP partly based on significantly increased risk with long-term exposure to EC with RR 1.30 (95%-CI: 0.78, 2.18) per 1 µg/m3 pooling 4 studies with high heterogeneity. The HEI Panel (99) concluded based on the dominance of positive associations considering other traffic related pollutants, the consistency in associations seen in the meta-analysis for $NO_2$, and the positive associations reported using indirect traffic measures, strongly points toward an association between TRAP and an increased risk of ALRI in children.

#### PAHs

Låg et al. (112) reported a limited number of studies suggesting a role of PAHs in the increased risk of respiratory infections.

### *Lung function & lung development*

#### $PM_{2.5}$

According to the US EPA ISA on PM (17), there was *limited evidence* for short-term effects of particulate matter on lung function. However, the evidence for impaired lung function growth with long-term exposure to $PM_{2.5}$ was *strong*. The overall assessment concluded a *likely to be causal relationship* for both, short-term and long-term exposure to $PM_{2.5}$. Garcia et al. (118) mentions two studies supporting lung-function decline with short-term exposure to $PM_{2.5}$ in children and two studies supporting effects on lower lung-function with long-term exposure.

#### $PM_{10}$

The US EPA ISA on PM (17) evaluated $PM_{2.5}$ and the fraction of $PM_{10}$ that does not contain $PM_{2.5}$. The evidence for respiratory health effects of $PM_{10}$-2.5 was considered *suggestive of a causal relationship* including lung-function. Garcia et al. (118) mentions two studies (different from the $PM_{2.5}$-studies) supporting lung-function decline with short-term exposure to $PM_{10}$ in children. The results of long-term studies showed mixed results.

#### $NO_2$

A *causal relationship* between respiratory health effects and short-term exposure to $NO_2$ have been proposed by the US EPA (25), partly based on studies showing associations between ambient $NO_2$ concentrations and lung function decrements in children with asthma which can lead to asthma

exacerbations. Evidence on effects in healthy children seem less consistent. Garcia et al. (118) reported more generally, that short-term elevations in $NO_2$ levels outdoors and indoors have been associated with reduction in child lung function.

Lung-function in children was *significantly* decreased with long-term exposure to $NO_2$ in a meta-analysis (8 ml lower FEV1 (95% CI: -14 to -1 ml) per 10 µg/m3 (independent from asthma status). A 10 µg/m3 higher in $NO_2$ level would translate into a 7% (95% CI: 4% to 12%) increase of the prevalence of children with abnormal lung function according to the authors (120). Publication bias was not detected. According to the US EPA (25), long-term $NO_2$ exposure is only *likely to have a causal relationship* with respiratory effects due to inconsistent results after co-pollutant adjustments e.g. with $PM_{2.5}$. Also, Barone-Adebesi et al. (120) interpret their results as effects associated with primary traffic emissions and not $NO_2$ per se.

#### Ozone

Short-term exposure to increased ozone exposure is *causally* related to decreases in lung-function in healthy children (23) with evidence stemming from panel studies with daily assessment of lung function in children attending summer camps. This is supported by the review of Holm et al. (119) which additionally concludes that long-term ozone exposure is associated with decreases in both lung function and lung function growth in children. However, according to Garcia et al (118) evidence on long-term effects are not consistent. Holm et al. (119) reported of a study showing a non-linear exposure response curve.

#### $SO_2$

The US EPA ISA (24) found weak and inconsistent evidence for an association between short-term $SO_2$ exposure and lung function impairment.

#### PAH

Låg et al. (112) found mixed results in studies on lung function in relation to PAH exposure. They rated the evidence as inconclusive.

### *Allergies*

#### $PM_{2.5}$/$PM_{10}$

Children with higher long-term exposure to $PM_{2.5}$ or $PM_{10}$ have an increased risk for allergic rhinitis, according to the analysis by Li et al. (135) combining 11 and 22 studies, respectively. Heterogeneity was high for the $PM_{10}$ studies and low for the $PM_{2.5}$ studies. Publication bias was present and trim-and-fill attenuated effect estimates slightly for $PM_{2.5}$. While $PM_{10}$ effect estimate became non-significantly increased. The authors state that risk in children might be higher than in adults. There was some evidence for an association of $PM_{2.5}$ with increased risk of sensitization to aeroallergens and food (125).

There was no association of eczema with prenatal $PM_{2.5}$ or $PM_{10}$ exposure in the review by Yue et al (122) without indication of publication bias. However, an exacerbation of disease was reported with short-term PM-exposure (123).The effect estimates of the two children studies included in the sub-group analysis by Chen et al. (124) indicated non-significant increases of conjunctivitis with short-term exposure to $PM_{2.5}$.

#### $NO_2$

Based on 24 studies, prevalence of allergic rhinitis was increased in children with higher $NO_2$ exposure OR 1.14 (1.07-1.22) per 10 µg/m3 with high heterogeneity of included studies. Publication bias was present but trim-and-fill did not alter overall association (135). There was some evidence for an association of $NO_2$ with increased risk of sensitization to aeroallergens and food (125).

Eczema risk was significantly elevated in children exposed to higher $NO_2$ exposure during pregnancy. Pooled risk estimates from 9 studies were RR 1.13 (1.06, 1.19) per 10 µg/m3 with no indication of

publication bias (122). An increase of eczema symptoms following short-term $NO_2$ exposure was reported by one study according to Abolhasani et al (123).

Conjunctivitis risk was elevated with short-term increases in $NO_2$-exposure combining three studies in children (124).

#### Ozone

Based on 9 studies, prevalence of allergic rhinitis was increased in children with higher ozone exposure OR 1.05 (1.01-1.09) per 10 µg/m3 with high heterogeneity of included studies. Publication bias was not detected.

Short-term increases in ozone exposure was associated with a significant increase in conjunctivitis risk in children combining three studies in children (124).

#### $SO_2$

Based on 16 studies, prevalence of allergic rhinitis was increased in children with higher $SO_2$ exposure OR 1.13 (1.03-1.24) per 10 µg/m3 with high heterogeneity between included studies. Publication bias was detected, but trim-and-fill did not alter overall association (even increased effect estimates) (135).

#### CO

Based on 8 studies, prevalence of allergic rhinitis might be increased in children with higher CO exposure, though pooled risks were not significantly increased (OR 1.08, 0.97-1.20) per 100 µg/m3 with high heterogeneity between included studies. Publication bias was not detected (135).

### *Asthma and asthma development*

#### $PM_{2.5}$ / $PM_{10}$

Bettiol et al. (127) found consistent evidence for an association of prenatal PM exposure and development of asthma in children. The evidence was less consistent for post-natal exposure. Meta-analysis was not attempted. However, Yan et al (128) reported a non-significantly increased risk of asthma onset with prenatal $PM_{2.5}$ exposure RR 1.06 (95%-CI: 0.98, 1.14) per 5 µg/m3 combining 4 studies with high heterogeneity and no publication bias detected. Whereas Han et al. (126) combined 15 studies, resulting in a significantly increased risk of $PM_{2.5}$-exposure with asthma onset without indication of publication bias. Restricting the analysis to cohort studies found even higher effect estimates with moderate heterogeneity OR 1.11 (95%-CI: 1.01, 1.22). An increment of exposure was not reported, though.

The US EPA (17) rated the relationship to be *likely causal* between respiratory outcomes and long-term exposure to $PM_{2.5}$. Even though the evidence from epidemiologic studies on asthma related outcomes was more limited, it indicated associations between long-term $PM_{2.5}$ exposure and asthma development in children, asthma prevalence in children, and childhood wheeze. The HEI (99) reported low to very low quality of evidence in the pooled traffic related PM-studies for prevalence of asthma ever, incidence of asthma (onset), and active asthma. The number of pooled studies was low (3-5 studies) and did not show significant associations.

#### $NO_2$ / NOx

According to the US EPA ISA (25), the relationship between long-term $NO_2$-exposure and development of asthma is *likely to be causal*. Newer evidence supports this judgement with the HEI traffic review (99) judging the evidence for asthma onset, asthma ever, and active asthma to be of moderate to high evidence. Evidence for a plausible monotonic exposure–response function was displayed in two studies on asthma-onset. The review by Han et al. (126) combining studies that also measured background $NO_2$-exposure as opposed to the strict traffic-related exposure studies in HEI (99) found significantly increased risk estimates without indication of publication bias. However, the increment of exposure is unclear.

#### EC

Asthma outcomes in association with EC-exposure were analyzed in the HEI review (99). The evidence for an association in the meta-analyses combining 3-5 studies was low to very low for all outcomes.

#### Ozone

While the US EPA ISA (23) reported a generally consistent evidence for associations of long-term ozone exposure with the development of asthma in children in epidemiological studies. The slightly older review by Zu et al. (130) including studies up to 2016 finds inconsistent evidence, further weakened by critical methodological limitations in statistical analyses and in exposure and outcome assessments, such as exposure measurement error and a lack of adjustment for key confounders.

The US EPA saw biologically plausible pathways through which long-term ozone exposure can lead to asthma development. However, Zu et al. (130) criticize lack of insight regarding an established mode of action.

#### $SO_2$

Associations of asthma outcomes with long-term $SO_2$ exposure have only been reviewed in the US EPA (24), ISAs finding most coherent evidence for an association with asthma development compared to other respiratory outcomes. Uncertainty remains in the adequacy of $SO_2$ exposure estimates and copollutant confounding resulting in a suggestive evidence rating for a causal relationship with asthma onset.

#### Other pollutants and sources

Buteau et al. (129) found indication of increased risks for asthma prevalence with proximity to industry, though effect estimates were not statistically significant. Han et al. (126) reported significantly increased risk for asthma development with benzene and VOC exposure without indication of publication bias. The latter however only combined 2 studies. The HEI review (99) pooled 3 CO-exposure studies in its analysis on ever asthma prevalence and saw significantly increased risks. However, study quality and evidence was considered low, which adds to the 2010 ISA assessment concluding there was inadequate evidence for long-term CO effects on respiratory morbidity. Studies on developmental effects from pre- and postnatal exposure to PAHs provided support for an association with asthma development in children according to Låg et al.(112) . The reported associations were not limited to B[a]P, but also encompassed low-molecular weight PAHs such as naphthalene, phenanthrene, and pyrene.

### *Asthma exacerbation and respiratory emergencies*

#### $PM_{2.5}/PM_{10}$

The US EPA (17) rated the relationship between short-term respiratory effects with $PM_{2.5}$ as causally related. Especially the relationship between between short-term $PM_{2.5}$ exposure and asthma-related hospital admissions and ED visits in analyses of children was strengthened in the latest report from 2019. The other reviews did not rate the level of evidence. However, they reported significantly increased risk with (1) short-term $PM_{2.5}$ exposure, combining 26 studies, showing a : a 5%, 95%-CI: 3-5% increased risk for asthma exacerbations with a 10 µg/m$^3$ higher short-term exposure (134) and (2) with $PM_{10}$, combining 11 studies, showing a 2.7%, 0.2-5.2% per 10 µg/m$^3$ higher short-term exposure to $PM_{10}$ (132). Heterogeneity was high. Additionally, Li et al (135) reported an increased risk for asthma exacerbation with exposure to ultrafine particles, combining 8 studies and concluding that the risk "might be increased" with UFP exposure. Risk of publication bias was low in all meta-analyses. The US EPA (17) reported a some evidence for a linear relationship for short-term $PM_{2.5}$ exposure and asthma hospital admissions and ED visits.

#### $NO_2$

The US EPA ISA (25) rated the evidence for short-term respiratory effects with $NO_2$ to be causally related. Additionally, multiple lines of evidence supported a relationship between short-term $NO_2$

exposure and asthma exacerbation. Zheng et al. (131) combined 24 children studies in their review and reported a significantly increased risk with $NO_2$ exposure. A short-term increase of $NO_2$-exposure by 10 µg/m3 increases hospital admissions and emergency department visits due to asthma by 2% (95%-CI: 1.1-2.9%). Publication bias was not detected. Heterogeneity of the subgroup results of children were not reported. However, evidence for all age-groups was rated high taking into account evidence for a concentration–response gradient.

#### Ozone

The 2020 US EPA ISA (23) rated the evidence for short-term respiratory effects with ozone to be causally related. This is based on strong evidence from epidemiologic studies demonstrating associations between ambient ozone concentrations and respiratory hospital admissions and ED visits, as well as panel studies that demonstrated associations of short-term ozone concentrations with respiratory symptoms in children with asthma. Animal toxicological studies aid in understanding of potential mechanisms underlying respiratory effects. The WHO review by Zheng et al (131) rated the evidence for an effect of ozone on ERV or HA due to asthma in all age groups as high, mentioning a concentration–response gradient and significantly increased risks with elevated short-term exposure to ozone, pooling 32 children studies with no indication of publication bias (RR 1.009; 95%-CI: 1.002, 1.017).

#### $SO_2$

The evidence for a relationship of short-term $SO_2$-exposure with asthma hospital admissions and emergency department visit is not as strong as for ozone or $NO_2$. The US EPA's ISA (24) saw a causal relationship primarily due to studies reporting positive associations for asthma hospital admissions and emergency department visits with short-term $SO_2$ exposures, specifically for children. However, the WHO review rates the quality of the evidence as *moderate* due to limitations in the study quality (131). The sub-group analysis revealed significantly increased risk in children but not other age groups (data not shown only for children).

#### CO

The US EPA ISA (32) rates the evidence for short-term effects of CO with respiratory outcomes as suggestive but not sufficient of a causal relationship. There is some epidemiological evidence, especially from children studies and toxicological studies demonstrating the potential for an underlying biological mechanism. However, controlled human exposure studies do not provide evidence to support CO-related health effects. The review by Huang et al. (134) reported significantly increased risks in children, combining six studies with moderate to high heterogeneity.

#### TRAP

The HEI traffic review (99) concluded from 12 mainly cross sectional studies, that evidence for exacerbation of asthma in children with long-term TRAP exposure was low. Meta-analysis was not possible due to limited overlap in pollutants.

### *4.4.4 Neurologic effects*

#### *Neurodevelopment and cognitive function*

#### $PM_{2.5}$

The HEI report (99) found eight studies investigating the association between cognitive function and traffic-related $PM_{2.5}$. Four studies report associations for attention and working memory. However, better verbal IQ and visual motor skills in a US cohort were paradoxically related with $PM_{2.5}$. Four studies reported null associations. None of the studies examined the dose-response function. Castagna et al. (139) confirms these results and concludes that robust results emerged for attention and executive functions like learning and memory functions, while Gartland et al. (138) evaluates the evidence for $PM_{2.5}$ as "mixed findings". Stenson et al. (136) found several significant associations between academic performance and $PM_{2.5}$, however, there were also three contradictory results

showing better performance and many null findings. The US EPA (17) saw limited and inconsistent epidemiologic evidence for neurodevelopmental outcomes in children. However, effects would be biologically plausible and effects in adults for cognitive impairment are more consistent.

#### Other PM

Two out of four studies reported an association with poorer general cognition and worse attention (99). There were no associations in four studies examining PMcoarse. The Spanish BREATHE cohort found associations of childhood exposure to ultrafine particles with impaired attention and working memory. There was no evidence for nonlinearity.

#### $NO_2$

14 studies examining cognitive function and $NO_2$ were included in the HEI review (99). Five European cohort studies found an association with at least one measure of cognitive function including poorer general cognition, lower verbal IQ, poorer attention and working memory. Four of those studies found no deviation from linearity in the exposure-response function. However, the majority of studies reported null associations across the different measures of cognitive function. Gartland et al. (138) assessed the evidence for $NO_2$ as weaker than for PM. A meta-analysis by Shang et al. (137) found no association between general cognitive function and language including two citations with 8, resp. 9 cohorts; Guxens et al. (392–394) analyzed several European cohorts. However, an increase of $NO_2$ during pregnancy was associated with global psychomotor and fine psychomotor function with small heterogeneity between studies. Publication bias could not be ruled out.

#### NOx

Three studies examined the general cognitive function and found no association with NOx (99).

#### PAH

Castagna et al. (139) found studies reporting associations between PAHs an IQ, performance IQ and verbal IQ (n=3), a study reporting negative associations with working memory in APOE e4 allele carriers and a study showing slower information processing speed during IQ testing.

#### Benzene

The HEI report (99) found no association in three European cohorts, except for a suggestive relationship of benzene with poorer infant mental development.

#### Ozone

Gartland et al. (138) included two studies that found no association between math or reading scores and ozone exposure. Stenson et al. (136) additionally included a study reporting poorer 3$^{rd}$ grade math scores associated with long-term ozone exposure.

#### Traffic indicators

The HEI report (99) found 10 studies examining traffic indicators. One out of six studies on distance to roadway found that shorter distance to roadway at birth was associated with lower verbal and nonverbal IQ. Significantly poorer cognitive function (executive function, verbal IQ, attention and working memory) was reported in 3 out of six studies. In to studies there was no evidence for the association between traffic density and language skills or attention and memory and one study even found a higher nonverbal IQ associated with higher traffic density.

### *Autism spectrum disorder*

#### $PM_{2.5}$ / $PM_{10}$

Lin et al found *strong evidence* for an association of post-natal $PM_{2.5}$ exposure in the first year of life and *moderate* evidence (in the second year) with ASD. The pooled risks were significantly increased (OR 1.69, 95%-CI: 1.22-2.15 and 3.13, 1.47-6.67) combining 9 and 3 studies. Heterogeneity was high for the former. Publication bias was explored and similar results were found. Evidence in the quality

of the studies was *very low or insufficient* for other exposure windows and exposure to $PM_{10}$. Dutheil et al. (141) reports similar findings regarding stronger association with post-natal than pre-natal exposures.

The US EPA (17) saw *limited evidence* in its report 2019 based on five studies despite generally positive associations (increased risks). Uncertainties remained regarding independent effects of $PM_{2.5}$ (from co-pollutants) and critical exposure windows. The HEI TRAP review (99) sees moderate-high confidence in an association with ASD, partly based on $PM_{2.5}$ reporting associations of prenatal or early life exposure with higher ASD risk.

#### $NO_2$ / NOx

Results of the meta-analysis by Dutheil et al. (141) show significantly increased risks with NOx exposure only in the optimistic models but not in the pessimistic models for both, pre-natal and post-natal exposures. With including two studies in the US EPA ISA (25) the evidence was limited. The HEI review on TRAP (99) saw moderate-high confidence in an association with ASD, partly based on $NO_2$ reporting associations of prenatal or early life exposure with higher ASD risk

#### Ozone

Based on 5 studies, the US EPA ISA (23) saw some epidemiologic evidence to suggest that prenatal or early life exposure to ozone may increase the risk for autism or autism spectrum disorder. However, overall evidence was limited including biological plausibility and lack of experimental animal studies showing effects in the brain that support the epidemiologic findings on autism.

### *ADD/ADHD*

#### PMs

Donzelli et al. (143) included 10 cohort and two cross-sectional studies with good quality according to the Newcastle-Ottawa scale. Eight of those studies reported odds ratios and six of them reported at least one statistically positive association. However, they observed high variability among studies and most studies were prone to have high risk of bias of exposure assessment. The authors concluded that there is *insufficient* evidence from epidemiological studies to support a causal association. Lin et al. (110) conducted a meta-analysis based on three cohort studies without heterogeneity and found no association between ADHD and $PM_{10}$ for the entire pregnancy period. Zhang et al. (142) also conducted a meta-analysis based on six studies, which were all included in the work of Donzelli et al. (143), and found no statistically significant increase in the risk of ADHD associated with PMs.

#### NOx

Based on five studies in the meta-analysis, Zhang et al. (142) found no association between ADHD and NOx. The heterogeneity between studies was moderate to high (68.4%). They found no indication of publication bias.

#### PAH

Three studies published between 2014 and 2017 were included in the meta-analysis by Zhang et al. (142) The risk of ADHD was not related with PAH exposure. There was minimal heterogeneity and no indication of publication bias.

#### TRAP

The HEI Panel (99) found low confidence in the presence of an association of TRAP with ADHD and related behaviors. There was a small amount of literature of TRAP and ADHD and related behaviors, with only eight studies representing seven cohorts in Europe and North America. Most studies reported null associations of pollutants with ADHD and related behaviors. The small number of studies that did find associations tended to find them with childhood exposure to EC and less so with $NO_2$ and $PM_{2.5}$. (99).

### *4.4.5 Cardiometabolic effects*

#### *Changes in glucose metabolism*

#### $PM_{2.5}$ / $PM_{10}$

Dang et al. (152) combined 3 and 4 studies regarding the association with HOMA-IR (homeostatic model assessment (HOMA) of insulin resistance, a metric derived from blood glucose and serum insulin measurements) and insulin levels, finding non-significant decreases and increases with $PM_{2.5}$ exposure. Pooled results for $PM_{10}$ indicated significant increases of HOMA-IR and insulin with $PM_{10}$, combining three and two studies, respectively. The 2019 US EPA ISA (17) concluded that evidence for a relationship between short- and long-term $PM_{2.5}$ exposure and metabolic effects is increasing. The limited number of studies and still inconsistent evidence from experimental studies especially on long-term effects led to a *suggestive of, but not sufficient to infer, a causal relationship* rating.

#### $NO_2$

Dang et al. (152) combined three studies each for HOMA-IR and insulin levels. Significant relationships were reported. The US EPA ISA on oxides of nitrogen (25) mentioned two children studies regarding metabolic effects. The overall evidence was rated as *suggestive of, but not sufficient to infer, a causal relationship*. The report seems to point to more gaps than the PM ISA regarding co-pollutant models and overall number of studies.

#### Ozone

None of the reviews considered ozone exposure except for the ISA (23). It concluded that effects of short-term ozone exposure are *likely to be causally* related to metabolic effects with consistent evidence from experimental and epidemiological studies,

#### Traffic pollution

Alderete et al. (153) discussed six studies in children. Even though the included only overweight and obese minority youth, the results suggest that increased air pollution exposure affects the underlying pathophysiology of type 2 diabetes, including insulin resistance and β-cell dysfunction in children.

#### *Overweight / Obesity*

#### $PM_{2.5}$ / $PM_{10}$

Maternal exposure to $PM_{2.5}$ as well as exposure to $PM_{2.5}$ and $PM_{10}$ during childhood was associated with a *significantly* increased risk of **obesity** in infants and children or adolescents, respectively. For example, obesity risk was increased by 24% (95%-CI: 9-41%, I2=99.5%) per 10 µg $PM_{2.5}$/m3 during childhood, obesity risk was less increased with maternal $PM_{2.5}$ exposure. Results were robust after trim-and-fill studying a possible publication bias. Heterogeneity in the meta-analyses by Lin et al. (110) was high. The authors discuss various factors for the observed heterogeneity stressing that they found higher risks in children and adolescents than in adults. PM1 and $PM_{10}$-2.5 were also associated with a higher risk of obesity (155,156). However, the number of studies was very low. Only two studies each with three estimates were pooled and found an increase in **BMI** associated with $PM_{2.5}$ and $PM_{10}$ exposure (156).

#### $NO_2$

Long-term exposure to $NO_2$ was associated with a *significantly* increased risk of obesity combining 11 estimates in Huang et al. (156): OR 1.11 (95%-CI: 1.06, 1.18) with no indication of publication bias. Heterogeneity between studies was high. BMI was significantly associated with $NO_2$. Combining five studies, BMI was increased by beta 0.03 (95%-CI: 0.01-0.04) per 1.06, 1.18 10 µg $NO_2$/m3 with medium heterogeneity. Wang et al. (157) reported an increased BMI in association with NOx combining 3 studies showing high heterogeneity. Publication bias was not assessed.

#### Ozone

Huang et al. (156) reported two studies that indicated elevated risks associated with long-term ozone exposure .

#### BC/soot

Parasin et al. (155) reported a significantly increased risk of obesity with $PM_{2.5}$abs. Three studies were pooled, with low heterogeneity. However, the increment of exposure was not reported.

#### Traffic measures

Various traffic measures showed *mixed* results in Wang et al. (157) with significantly elevated risks with annual average daily traffic volumes, pooling two studies from the US.

#### *Blood pressure*

#### $PM_{2.5}$ / $PM_{10}$

The pooled analysis by Yan et al (158) of long-term exposure to particulate matter, including 8 to 9 studies, showed increases in systolic and diastolic blood pressure for both measures of particulate matter. Heterogeneity was low for the $PM_{2.5}$ analysis showing more pronounced effects than with $PM_{10}$ exposure; e.g. 1.8 mmHg (0.94-2.65) increases of systolic blood pressure per 10 µg $PM_{2.5}/m^3$ vs. 0.5 mmHg (0.19, 0.81) per 10 µg $PM_{10}/m^3$ exposure. Publication bias was not detected. An increased risk for childhood hypertension was reported for $PM_{10}$ as well with low heterogeneity between the included 4 studies. Associations with short-term exposures in relation to blood pressure measures were reported but no pooled analysis was conducted due to low numbers of studies, except for $PM_{10}$, showing air pollution dependent increases. Publication bias was detected and trim-and-fill was conducted without reporting of results.

#### $NO_2$

The diastolic blood pressure was significantly increased with long-term exposure, pooling results of 5 studies. A non-significant increase was reported for the association of systolic blood pressure with $NO_2$. No publication bias was detected. The number of studies was too low for an analysis of short-term effects (128).

#### Ozone

Evidence on effects of ozone exposure on blood pressure stems from three Asian studies as reported in Yan et al. (158). Two studies reported increases in systolic blood pressure in association with long-term exposure to ozone. Results in diastolic blood pressure were mixed. The risk of hypertension was increased with long-term ozone exposure according to the two studies. One study also reported increases of systolic and diastolic blood pressure with short-term ozone exposure.

#### $SO_2$

Evidence on effects of $SO_2$ exposure on blood pressure stems from four Asian studies with inconsistent results regarding hypertension risk, long-term effects on both, systolic and diastolic blood pressure. Only one study in the review by Yan et al. (158) reported increase of systolic blood pressure with short-term $SO_2$-exposure.

### *4.4.6 Leukemia*

#### *$PM_{2.5}$*

Six studies were included in the review by Wei et al. (159) showing a non-significantly increased risks.

#### *$PM_{10}$*

Only two studies in the review by Wei et al. (159) indicated non-significantly increased risks with large confidence intervals.

#### *$NO_2$*

The risk for leukemia was *significantly* increased with $NO_2$ exposure (159). The separate analyses for acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) did not find differences in leukemia risk with $NO_2$. The evidence level was not assessed. However, Wei et al. (159) reported a clear dose-response relationship and publication bias was not detected. No association with NOx.

#### *Benzene*

The risk for leukemia was *significantly* increased with Benzene exposure (159).The separate analyses for acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) indicated higher Benzene related risks for AML (effect estimates 1.61 vs. 1.07). The evidence level was not assessed. However, Wei et al. (159) reported a clear dose-response relationship. Publication bias was detected and results after trim and fill method were attenuated and no longer significantly increased.

#### *Traffic density*

The meta-analysis for leukemia with higher traffic density including 16 studies showed *significantly* increased risks (161). The separate analyses for acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) did not find differences in leukemia risk. The evidence level was not assessed. Dose-response analysis showed a steep increase in risk when living closer than 150m to a trafficked road. Publication bias could not entirely be ruled out.

## List of abbreviations

| Abbreviation | Name | Reference |
|---|---|---|
| AAR | Ask, Advise, Refer | |
| ADD / ADHD | Attention deficit disorder / attention deficit hyperactivity disorder | |
| AIR | German Committee on Indoor Air Guide Values | |
| ALL | Acute lymphocytic leukemia | |
| ALRI | Acute lower respiratory infections | |
| AML | Acute myeloid leukemia | |
| AQG | Air quality guidelines | |
| ASD | Autism spectrum disorder | |
| ATSDR | Agency for Toxic Substances and Disease Registry | |
| BC | Black carbon | |
| beta | Refers to a direct effect measure, e.g. change in blood pressure in mmHg | |
| BfR | German Federal Institute for Risk Assessment (in German, Bundesinstitut für Risikobewertung) | |
| BMI | Body mass index | |
| CI | Confidence interval | |
| CO | Carbon monoxide | |
| $CO_2$ | Carbon dioxide | |
| DIY | Do it yourself | |
| ECHA | European Chemicals Agency | echa.europa.eu/ |
| EE | Effect estimate | |
| EEA | European Environment Agency | www.eea.europa.eu |
| EHR | Electronic health record | |
| EMR | Electronic medical record | |
| EOT | End-of-treatment | |
| ERV | Emergency room visits | |
| ETC-HE | European Topic Centre- Human health and the Environment | www.eionet.europa.eu/etcs/etc-he |

| Abbreviation | Name | Reference |
|---|---|---|
| EU | European Union | |
| FAQ | Frequently asked questions | |
| FE | Random effects meta-analysis model | |
| FEV1 | Forced expiratory volume (FEV) in 1 second, refers to the volume of air that an individual can exhale during a forced breath in 1 second, a measure of lung function | |
| GDP | Gross domestic product | |
| GME | 'Gesundheits monitoring einheiten' | |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation, a quality assessment tool and approach | |
| HA | Hospital admission | |
| HEPA | High-efficiency particulate air | |
| HOMA-IR | Homeostasis model assessment-estimated insulin resistance | |
| HRAPIE | Health risks of air pollution in Europe | |
| HSB | Home smoking ban | |
| IAQ | Indoor air quality | |
| IARC | International Agency for Research on Cancer | https://www.iarc.who.int/ |
| M | Integrated pest management | |
| ISA | Integrated science assessment | |
| JBI | Joanna Briggs Institute, a tool for study quality assessment | |
| KiSS | Kids safe and smoke-free | |
| LBW | Low birth weight | |
| LRTI | Lower respiratory tract infections | |
| LT | Long-term exposure | |
| LRI | Lower respiratory tract infections | |
| LUDOK | Lufthygienische Dokumentationsstelle am Swiss TPH, database and service | https://www.swisstph.ch/en/projects/ludok |

| Abbreviation | Name | Reference |
|---|---|---|
| | regarding health effects of air pollution | |
| MI | Motivational interviewing | |
| $NO_2$ | Nitrogen dioxide | |
| NOS | Newcastle Ottawa scale | |
| NOx | Nitrogen oxides, these include NO and $NO_2$ | |
| NR | Not reported | |
| NTP-OHAT | National Toxicology Programme Office for Health Assessment and translation | |
| $O_3$ | Ozone | |
| OM | Otitis media | |
| OR | Odd ratio | |
| PA | Physical activity | |
| PAHs | Polycyclic aromatic hydrocarbons | |
| PB | Publication bias | |
| PECO/PICO | Population, Exposure/Intervention, Comparator and Outcomes | |
| PEF | Peak expiratory flow | |
| PM | Particulate matter | |
| $PM_1$ | Particulate Matter with a diameter of 1 µm or smaller | |
| $PM_{10}$ | Particulate matter with a diameter of 10 micrometers or smaller | |
| $PM_{10-2.5}$ | Particulate Matter with a diameter between 2.5 and 10 µm | |
| $PM_{2.5}$ | Particulate matter with a diameter of 2.5 micrometers or smaller | |
| $PM_{2.5abs}$ | $PM_{2.5}$ absorbance a measure for soot in particulate matter | |
| PMs | Various metrics of particulate matter | |
| ppm | Parts per million | |
| PTB | preterm birth | |

| Abbreviation | Name | Reference |
|---|---|---|
| RAC | Risk Assessment Committee | |
| RCT | Randomized control trial | |
| RE | Random effects meta-analysis model | |
| RoB | Risk of bias | |
| RR | Relative risk | |
| SBAT | School based asthma therapy trial | |
| SGA | Small for gestational age | |
| SHS | Secondhand smoke | |
| SIDS | Sudden infant death syndrome | |
| $SO_2$ | Sulfur dioxide | |
| ST | Short-term exposure | |
| TiRO | Take it right outside | |
| TRAP | Traffic-related air pollution | |
| TSE | Tobacco smoke exposure | |
| TVOCs | Total volatile organic compounds | |
| UFP | Ultrafine particles, particles with a diameter less than 100 nanometers | |
| UN | United Nations | www.un.org |
| UNEP | United Nations Environment Programme | www.unep.org |
| UNICEF | United Nations Children's Fund | www.unicef.org |
| URTI | Upper respiratory infections | |
| US EPA | United States Environmental Protection Agency | www.epa.gov |
| VOCs | Volatile organic compounds | |
| WHO | World Health Organization | www.who.int |
| z-score | z-score is the standard deviation (SD) above or below the mean, a statistical measure to understand deviations from a mean in a given population | |

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