

Environmental inequality: air pollution and asthma in children

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Running title: Air pollution and asthma in children

Abstract:

Introduction: Whether you benefit from high-quality urban environments, such as those rich in green and blue spaces, that may offer benefits to allergic and respiratory health depends on where you live and work. Environmental inequality, therefore, results from the unequal distribution of the risks and benefits that stem from interactions with our environment.

Methods: Within this perspective, this article reviews the evidence for an association between air pollution caused by industrial activities, traffic, disinfection-by-products and tobacco/e-cigarettes and asthma in children. We also discuss the proposed mechanisms by which air pollution increases asthma risk, including environmental epigenetic regulations, oxidative stress, and damage, disrupted barrier integrity, inflammatory pathways, and enhancement of respiratory sensitization to aeroallergens.

Results and conclusions: Environmental air pollution is a major determinant of childhood asthma, but magnitude of effect is not shared equally across the population, regions, and settings where people live, work, and spend their time. Improvement of the exposure assessment, a better understanding of critical exposure time windows, underlying mechanisms, and drivers of heterogeneity may improve the risk estimates. Urban conditions and air quality are not only important features for national and local authorities to shape healthy cities and protect their citizens from environmental and health risks, but they also provide opportunities to mitigate inequalities in the most deprived areas where the environmental burden is highest. Actions to avoid exposure to indoor and outdoor air pollutants should be complementary at different levels – individual, local, and national levels – to take effective measures to protect children who have little or no control over the air they breathe.

Key Message

- The effect of environmental air pollution on childhood asthma varies across populations, regions, and residential settings.
- Improvement of the exposure assessment, a better understanding of critical exposure windows and underlying mechanisms may provide more homogenous risk estimates for childhood asthma associated with environmental pollution.
- Urban planning and air quality monitoring provide opportunities to mitigate inequalities in the most deprived areas where the environmental burden is more significant.

- Actions to avoid exposure to indoor and outdoor air pollutants should be conducted, particularly in high risk environments, to protect children who have little or no control over the air they breathe.

1. Introduction

Dirty air is now recognized as the single biggest environmental threat to human health [1]. The air we breathe is becoming increasingly polluted and its impact on health is appraised to be as great as other major global health risks such as unhealthy diet, sedentarism, or tobacco. Nonetheless, air pollution is hard to escape. An emerging body of evidence emphasizes the associations between poor-quality environments and socioeconomic conditions at both local and regional scales [2]. Whether you benefit from high-quality urban environments, such as those rich in green and blue spaces, that may offer benefits to allergic and respiratory health depends on where you live and work. Environmental inequality, therefore, results from the unequal distribution of the risks and benefits that stem from interactions with our environment.

There are several dimensions of environmental inequality. First, the imbalanced distribution of negative and positive impacts. The helpful effects of infrastructure such as an industry often affect much broader scales than its adverse influences such as pollution [3]. Secondly, the distribution of environmental risks remains in time with future generations facing the risks created by the dirtying activities of today. Infants whose mothers have been exposed to higher levels of air pollution during pregnancy are much more likely to develop asthma [4]. Thirdly, who produces air pollution and who undergoes the consequences follows at many stages and is a driver of inequity. For instance, the environmental footprint for Europe is over twice the size of its capacity to produce beneficial biological materials and to engross waste materials [5]. Thus, much of the impact manifests not in the region's carbon footprint but outside and with implications for the health of persons living in those environments. A fourth dimension relates to public participation in decision-making and access to justice when the topic is air pollution. This social media dimension is of major importance nowadays. Public awareness drives political and social measures to pressure to tackle air pollution. Finally, methods of assessment of exposures to air pollution are complex and challenging and not within our scope. A brief overview of both direct and indirect approaches as well as their strengths and limitations are presented in supplementary online table S1.

Environmental inequalities are not a novel phenomenon. Conditions of social vulnerability in education, income, or access to health coupled with air pollution exposure

have been present for a long time. But a different perspective is presented in this article, arguing for the case of air pollution and asthma as one of the features of environmental inequality. In a rapidly changing world, economic development and industrial activities, traffic-related air pollution (TRAP), urbanization, and indoor pollutants exposure, together with rapid population growth, are major driving forces of air pollution and climate change [6] that all impact asthma risk in children. Within this perspective, this article aims to answer (i) what is the evidence for an association between air pollution caused by industrial activities, traffic, disinfection-by-products and tobacco/e-cigarettes and asthma in children? (ii) what the proposed mechanisms behind this association are, and finally, (iii) what can be done to mitigate the burden of air pollution on asthma.

2. Environmental pollutants as determinants of childhood asthma

2.1. Outdoor air pollution from industrial activities

Industrial activities are characterized by frequent emissions of air pollutants such as carbon dioxide (CO₂), sulfur (SO_x) and nitrogen oxides (NO_x), particulate matter (PM), heavy metals, and volatile organic compounds (VOCs) [7]. Consequently, and although the aetiology of allergic diseases is continuously evolving as novel information is unveiled by epidemiological studies, an association between allergy and industrialization has long been perceived. Back in 1996, Schäfer and co-workers published a study where they compared the prevalence of allergic diseases in preschool children from different parts of Germany and observed a significantly higher risk of atopic eczema in the East when compared to a countryside town in the West [8]. Authors argued this difference could potentially be explained by the characterization of pollutants in each region, with more sulphurous air pollution in Eastern industrial areas when compared to a more oxidizing Western air pollution [8, 9]. Since then, several findings of associations between industrial pollution and asthma started to emerge. Children living in areas characterized by higher industrial pollution were found to have a 5% increase in the risk of developing asthma [10]. Emergency department visits for asthma, and particularly pediatric asthma, were also found to be significantly higher [11, 12]. The more frequent exacerbations in patients with asthma living in industrial areas may also be explained by the impact of the pollutants on lung function. As an example, peak expiratory flow and forced vital capacity were found to be significantly hampered by exposure to particulate matter and NO_x [13].

However, it is still not clear when the relevant window of exposure to industrial pollution occurs. Which period of exposure (prenatal, perinatal, early-life and/or most recent) has

the most determinant associations? How much is gestational exposure relevant to the industrial exposome? Although there are few longitudinal studies focused on early-life exposure to industrial pollution, there is evidence that children living in neighborhoods with industrial facilities, from birth, are at a higher risk of chronic respiratory morbidity [14]. Despite the eventual overlapping of effects from TRAP, studies have shown that industrial pollution alone can be a significant and independent determinant of asthma in early life [15, 16]. The combination of both sources, however, could be even more deterministic during childhood [14], since it has been shown that PM_{2.5} exposure (largely associated with TRAP) in combination with secondary sulphate sources (mainly related to industrial activity) was found to significantly exacerbate respiratory symptoms in children [17].

Although it is possible to hypothesize, based on other exposure factors, that gestation would be a determinant window of exposure to industrial pollution, there is no strong definitive evidence of such. One retrospective study showed that preschool children whose mothers worked at an industrial facility were at a higher risk of wheezing [18]. However, these mothers, and consequently their children, would be more likely to live near industrialized areas (closer to workplace), which could potentially confound the proper estimation of the relevant window of exposure.

The level of urbanization associated with industrialized zones may also be an important factor behind the different magnitude of observations in published studies. By analyzing air pollution data from air quality stations across Europe [19], it is possible to conclude that most pollutants associated with industrial zones are, on average, at higher levels in urban and suburban environments when compared to rural areas (**Figure 1**). This difference may not only be attributed to the higher density of industrial activity in urban and suburban zones but may also reflect the protective effect of greener rural areas against environmental pollutants. Hence, it is possible to hypothesize that these two factors –industrialization and geographical area– may partially explain the increased prevalence of asthma in urban settings and the heterogeneity in observations between different studies [20, 21].

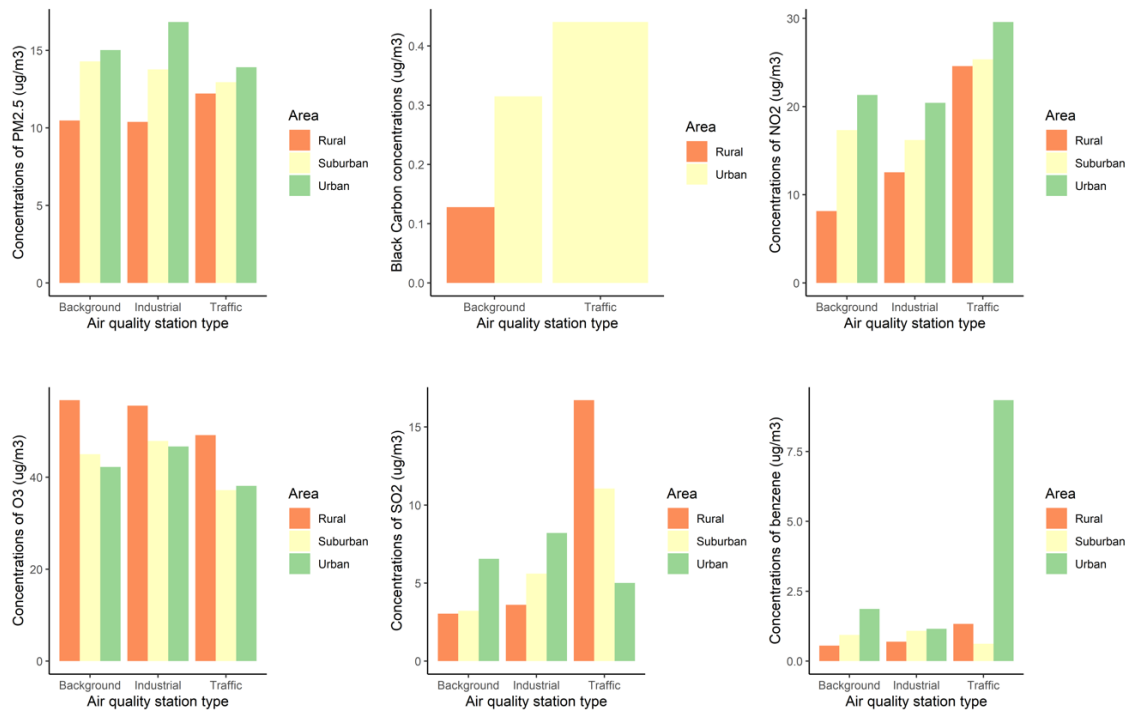


Figure 1. Average concentrations of air pollutants measured in air quality stations across the EU in 2022 according to urbanization level

Traffic stations: located close to a single major road; industrial stations: located close to an industrial area/source; background stations: located where pollution levels are representative of the average exposure of the general population or vegetation. Urban areas: continuously built-up urban areas; suburban areas: largely built-up urban areas; rural areas: all other areas. European air quality information is reported by EEA member countries, including all EU Member States, and EEA cooperating and other reporting countries. Data retrieved from Air Quality e-Reporting database (<https://www.eea.europa.eu/data-and-maps/data/aqereporting-9>).

2.2. Traffic-related air pollution and childhood asthma

In December 2020 a court in the United Kingdom made history by ruling acute respiratory failure, severe asthma, and exposure to pollution as one of the causes of the death of a 9-year-old child. The verdict confirmed the need for legislation and proper implementation: it was the illegal levels of air pollution listed among failures to reduce levels of NO₂ which possibly contributed to her death. Ella Kissi-Debrah's lived near a busy road in London with her mother and has become the first person in the UK –and potentially the world– for whom air pollution has been listed as a cause of death [22].

The health costs of air pollution are clear: in 2019 about one in 12 new child asthma cases worldwide may be attributable to NO₂ pollution [23]. Although these figures have been even worst in the past, with a global decline in the last decade of the NO₂-attributable fraction of pediatric asthma incidence from 19.8% in 2000 to 16.0% in 2019, the regional trends remain heterogenous with urban average attributable fractions

declining in high-income countries, Latin America and the Caribbean, central and eastern Europe, central, southeast, and east Asia, and Oceania, and escalating in south Asia, sub-Saharan Africa, and North Africa and the Middle East [23].

Vehicle emissions usually mean TRAP, which contains a combination of vehicle exhausts, secondary pollutants, and noncombustion emissions such as road dust (Figure 2). Since the difficulty in measuring all the components of TRAP, pollutant surrogates such as measured or modeled concentrations of PM_{2.5} and PM₁₀ and gases such as NO₂, nitric oxide (NO), NO_x, and ozone (O₃), and direct measures of traffic, including proximity/distance of the residence to the main road and traffic volume within the buffer are used. Diesel exhaust particles (DEPs) are generated through the combustion of diesel fuel by vehicles or diesel-powered equipment. Exposure occurs in both environmental and occupational settings and is of particular concern as air quality and engine exhaust control policies are still to produce significant changes in TRAP levels [24]. DEP consists of a carbon nanoparticle core with a complex mixture of metals and organic chemicals that are adsorbed onto their surface and responsible for most of the deleterious effects.

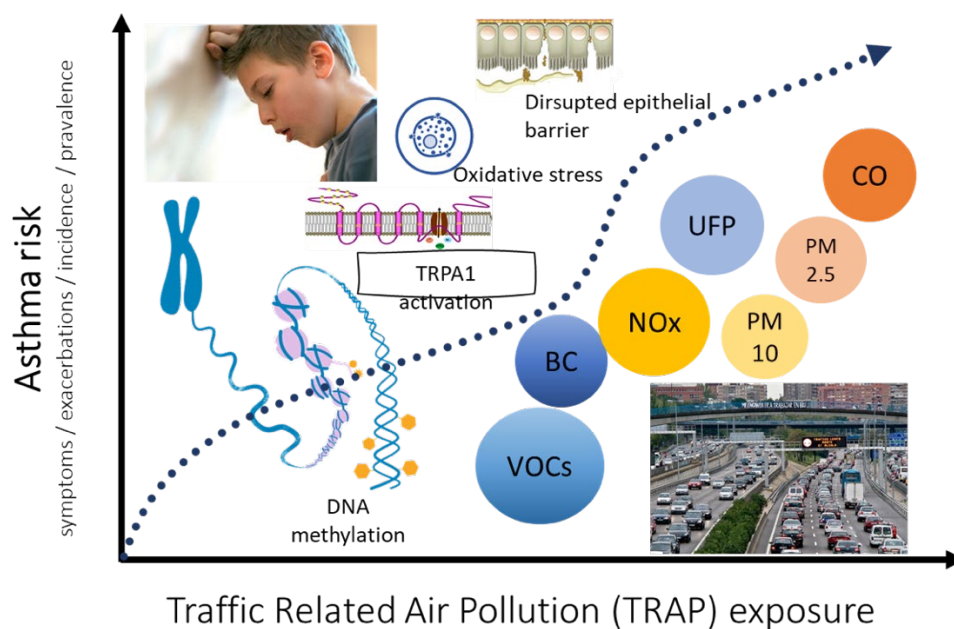


Figure 2. Mechanistic insights into TRAP exposure and the pathogenesis of asthma

BC, for black carbon; CO, carbon monoxide; EC, elemental carbon; NO_x, nitrogen oxides: nitrogen dioxide; PM_{2.5}, particulate matter < 2.5 µm in diameter; PM₁₀, particulate matter < 10 µm in diameter, PM coarse, particulate matter between 2.5 and 10 µm in diameter; TRAP, traffic-related air pollutants; TRPA 1, transient receptor potential ankyrin 1; TVOCs, total volatile organic pollutants; UFP, ultra-fine Particles

The impact of prenatal exposures to NO₂, SO₂, and PM₁₀ on subsequent risk of wheezing and asthma development in childhood has been well documented [25]. Recently it was shown that not only do black carbon (BC) particles from environmental exposure reach the fetal side of the human placenta, but further correlate with the mothers' residential BC exposure averaged over the entire pregnancy [26]. A pooled analysis of two pregnancy cohorts showed that higher exposure to PM_{2.5} during the sacral phase of fetal lung development was associated with a higher risk of asthma, particularly among those without a maternal history of asthma [27]. Although this is in line with previous observations in two different birth cohorts, where an increase per 2 µg/m³ of PM_{2.5} exposure during mid-gestation was associated with a 4% increase in the hazard ratio for childhood asthma diagnosis [28, 29], discrepancies exist for PM_{2.5} windows of exposure based on phases of fetal lung development. Others reported a critical period as early as the 6 weeks including both the pseudoglandular and canalicular phases of lung morphological development suggesting during early pregnancy an impact of pollutants on branching morphogenesis [29]. Yet, as much immune development occurs later in gestation, the critical period for the association between PM_{2.5} and elevated cord serum total IgE has not surprisingly been suggested to occur between months 6th and 7th of pregnancy [30]. Moreover, children born to mothers reporting elevated stress in pregnancy and with higher PM_{2.5} exposures between 19 and 23 weeks of gestation were significantly more likely to develop asthma, particularly if they were boys [31].

Although the heterogeneity across studies may limit the ability to draw conclusions, it seems from the overview of meta-analyses that TRAP exposure is associated with both the development and exacerbation of asthma in children (**Table 1**). These findings are limited by diverse definitions in exposure (land-use regression/dispersion models and roadway proximity), outcomes (asthma symptoms, asthma diagnosis, wheeze phenotypes or allergic sensitization), unmeasured confounding of other factors (environmental allergens, climate, diet, physical activity or socioeconomic) and their complex interactions that drive allergic disease and modify the effects of TRAP exposure. A recent overview of systematic reviews and meta-analysis that focused on children's TRAP exposures as a potential cause for asthma development found an increased risk of 7% for PM_{2.5}, 11% for NO₂, 21% for benzene, and 6% for TVOCs [32]. Additionally, DEP exposure at age one was positively associated with aeroallergen sensitization at ages two and three [33]. Compared with NO₂, PM_{2.5} has been more strongly associated with outdoor aeroallergen sensitization while exposure to both NO₂ and PM_{2.5} has been significantly associated with food sensitization at the age of 4 and

8 years [34]. There was some evidence that childhood exposure to TRAP may also be associated with increased risks of eczema and hay fever [34].

Table 1. Overview of systematic reviews on the association between traffic-related air pollution (TRAP) and childhood asthma

Author	Studies / participants	Exposure/intervention (n studies)	Comparator/assessments	Outcomes
Kun Han <i>et al.</i> , 2021 [32]	27 studies: 19 cohort, 7 cross-sectional, and 1 case-control. 16 conducted in Europe, 2 in North America, 9 in Asian countries	PM2.5 (15); NO2 (22); benzene (4) and TVOCs (2)	ISAAC or ATS questionnaires to understand respiratory symptoms and asthma	TRAP increased the risk of asthma among children: PM2.5 (meta-OR = 1.07, 95% CI:1.00; 1.13), NO2 (meta-OR = 1.11, 95% CI:1.06; 1.17), Benzene (meta-OR: 1.21,95% CI:1.13; 1.29), TVOCs (meta-OR:1.06, 95% CI: 1.03; 1.10)
Bettiol <i>et al.</i> , 2021 [35]	26 studies: based on 21 pregnancy or birth cohorts, and 2 case-control. 10 conducted in Europe, 8 in North America, 2 in Asian countries and 1 in Mexico	PM10, PM2.5, PM coarse, and NO during pregnancy and the first 2-years of the child's life	Follow-up periods varied according to the outcome, ranging from 6 to 48 months for wheezing and from 2 to 10 years for asthma, though in the majority of studies on asthma incidence children were followed up at least up to school age.	The second trimester of pregnancy seemed to be particularly critical for asthma risk. As for exposure during early life (15 cohorts), most studies found a positive association between PM (7/10 studies) and NOx (11/13 studies) and the risk of asthma development, while the risk of wheezing development was controversial.
Khreis <i>et al.</i> , 2017 [36]	41 studies: 31 cohort, 6 case-control, and 4 cross-sectional	BC, CO, NOx, NO, NO2, PM2.5, PM10, PM coarse, and UFPs	Risk of asthma reported as incidence or lifetime prevalence from birth until 18 years old	Positive and statistically significant associations between asthma onset and the exposure to BC, NO2, PM2.5 and PM10, with the least heterogeneity detected in the BC and PM analyses and the most detected in the NO2 and NOx analyses.
Lau <i>et al.</i> , 2018 [37]	7 studies: all cohort studies Canada, France, USA, Sweden, Netherlands, and Norway	CO, NO2, NOx, PM2.5, and PM10	Childhood asthma and wheezing phenotypes	TRAP is associated with the development of childhood transient and persistent asthma/wheezing phenotypes but may not be associated with late-onset asthma/wheezing. Associations were inconsistent and interpretation of the results should be drawn cautiously

G. Bowatte <i>et al.</i> , 2015 [34]	19 studies: 11 birth cohorts 7 in Europe and 4 in North America	BC, NO ₂ , NO _x , PM _{2.5} , and PM ₁₀	Asthma, wheeze, eczema, hay fever and sensitization to allergens	TRAP increased the risk of asthma in childhood: PM _{2.5} : OR 1.14, 95%CI 1.00; 1.30 per 2mcg/m ³ BC: OR 1.20, 95%CI 1.05; 1.38 per 1*10 ⁻⁵ m ⁻¹ Early childhood exposure to TRAP is associated with the development of asthma up to 12 years of age. Increasing exposure to PM _{2.5} is associated with allergic sensitization
Favarato <i>et al.</i> , 2014 [38]	18 studies	NO ₂ at home (12) and/or school (8)	Asthma symptoms/ diagnosis by questionnaire	NO ₂ : OR: 1.06 (95 % CI: 1.00; 1.11)
H. R. Anderson <i>et al.</i> , 2013 [39]	16 birth cohorts Based in Europe (11) or North America (5).	BC, NO ₂ , NO _x , O ₃ , PM _{2.5} , and PM ₁₀ O ₃ , SO ₂	Incidence of asthma (11), the incidence of wheeze (5), lifetime prevalence of asthma (4) and lifetime prevalence of wheeze (3)	NO ₂ : OR 1.07 (95% CI: 1.02; 1.13) per 10 µg/m ³ . PM _{2.5} : OR 1.16 (95% CI: 0.98; 1.37) per 10 µg/m ³ . Estimates were reduced in size and statistical significance by adjustment for publication bias but remained positive
Gasana <i>et al.</i> , 2012 [40]	19 included: 10 cross-sectional. and 9 cohort studies, 9 conducted in Europe, 5 in North America, 4 in Asia, 1 in Latin America	CO, NO, NO ₂ , SO ₃ , O ₃ , PM _{2.5} , and PM ₁₀	ISAAC questionnaires to understand respiratory symptoms and asthma and/or physician diagnosis of asthma and wheeze	TRAP increased the risk of asthma in childhood: NO ₂ (meta-OR: 1.05, 95% CI: 1.00; 1.11), NO (meta-OR: 1.02, 95% CI: 1.00; 1.04), CO (meta-OR: 1.06, 95% CI: 1.01; 1.12) and of a higher prevalence of wheeze in children: SO ₂ (meta-OR: 1.04, 95% CI: 1.01; 1.07) PM (meta-OR: 1.05, 95% CI: 1.04; 1.07)

Abbreviations: BC, black carbon; CO, carbon monoxide; EC, elemental carbon; NO_x, nitrogen oxides: nitrogen dioxide; SO₂, sulfur dioxide; O₃, ozone; PM_{2.5}, particulate matter < 2.5 µm in diameter; PM₁₀, particulate matter < 10 µm in diameter, PM coarse, particulate matter between 2.5 and 10 µm in diameter; TRAP, traffic-related air pollutants; TVOCs, total volatile organic pollutants; UFP, ultra-fine particles.

2.3. Cleaning and consumer products and childhood asthma

While the development of synthetic chemical compounds has improved our daily life, the role of exposure to detergents, cleaning, and consumer products in human health has increased in past years with exposure implicated in the development of several human diseases, such as asthma [41].

Occupational exposure to cleaning products and disinfectants during pregnancy may affect the fetus at a critical time window [42]. Maternal exposure starting before conception and continuing is associated with an approximately two-fold increased risk of childhood asthma and/or wheeze [42]. This is particularly evident for phthalate exposure for which even low-level exposure in early life was associated with up to a fourfold increase in the risk of asthma and recurrent wheeze at 5 years of age in a dose-dependent manner [43]. Similarly, the use of PVC flooring or wall covering has been reported to be associated with the development of asthma among children and endocrine-disrupting chemicals exposure in classrooms may not only impact obesity risk but also the pathogenesis of the obesity and asthma phenotype through a process mediated by the autonomic nervous system [44]. Evidence supports that environmental and occupational exposures may be associated with epigenetic changes that may be transmissible to offspring, resulting in inherited changes in gene expression in children of exposed mothers [45], and consequently affecting the modulation of immune responses and increasing the susceptibility to develop asthma.

Chlorine bleach or sodium hypochlorite is the most used disinfecting and cleaning agent, and chlorine disinfection-by-products (DBPs), such as chlorine or trichloramine, are irritants to the respiratory tract and are also associated with acute lung injury [46]. A recent position paper on the evidence of the health effects of acute and chronic exposure to swimming pools suggested that early and chronic exposure to DBPs may be associated with a higher risk of childhood asthma [47]. Taken together the evidence supports a growing call for mitigation and prevention actions on the role of cleaning and consumer products on childhood asthma. Further studies are also needed to evaluate the longer-term effects of low-to-higher exposure to such products early in life on asthma at younger ages.

2.4. Tobacco and e-cigarettes exposure and childhood asthma

According to WHO, exposure to second-hand smoke (SHS) kills around 1.2 million people every year and 65,000 of these premature and preventable deaths are in children under 15 years. A recent meta-analysis of 93 studies examining the effect of SHS exposure reported a significantly positive association between SHS exposure and

doctor-diagnosed asthma in children [48] (**Table 2**). Although prenatal has a greater impact than postnatal exposure on childhood asthma, the combined effect of maternal smoking during and after pregnancy was higher. A pooled analysis based on data from European birth cohorts suggested a linear dose-response association between maternal daily cigarette consumption and increased childhood asthma [49]. Children exposed to ≥ 10 cigarettes/day during pregnancy had an increased risk of early transient and persistent asthma [50].

Table 2. Overview of the studies on the association between second-hand smoke (SHS) and childhood asthma

Author	Year	Study	Exposure measurement	Outcomes
He <i>et al.</i> [48]	2020	meta-analysis (93 studies)	SHS exposure	<p>the positive association between SHS exposure and doctor-diagnosed asthma in children (OR=1.24, 95% CI: 1.20; 1.28)</p> <p><i>prenatal exposure</i>: OR=1.25, 95% CI: 1.16; 1.33</p> <p><i>postnatal exposure</i>: OR=1.24, 95% CI: 1.20; 1.28</p> <p><i>maternal smoking during and after pregnancy</i>: OR=1.38, 95% CI: 1.11; 1.65</p> <p><i>exposure at different ages</i>:</p> <p>0-2 years old: OR=1.45, 95% CI: 1.24; 1.65</p> <p>3-6 years old: OR=1.23, 95% CI: 1.16; 1.30</p> <p>7-14 years old: OR=1.22, 95% CI: 1.14; 1.30</p> <p>15-18 years old: OR=1.11, 95% CI: 0.91; 1.31</p>
Thacher <i>et al.</i> [50]	2018	5 European birth cohort studies (n=10 860 participants)	maternal smoking	exposure to ≥10 cigarettes/day and early transient and persistent asthma: OR=2.07 (95% CI 1.60-2.68) and OR=1.66 (95% CI: 1.29; 2.15), respectively
Neuman <i>et al.</i> [49]	2012	8 European birth cohorts (n=21 600 children)	Maternal daily cigarette consumption	childhood asthma (OR=1.65, 95% CI: 1.18; 2.31)
Mitchell <i>et al.</i> [56]	2012	Cross-sectional study including 220 407 children (6-7 years of age) from 75 centres in 32 countries and 350 654 adolescents (13-14 years of age) from 118 centres in 53 countries	current paternal smoking	<p>positive association between SHS exposure and asthma at different ages:</p> <p>6-7 years old: OR=1.11, 95% CI: 1.06; 1.15</p> <p>13-14 years old: OR=1.08, 95% CI: 1.04; 1.12</p> <p>and with severe asthma symptoms</p> <p>6-7 years old: OR=1.23, 95% CI: 1.16; 1.30</p> <p>13-14 years old: OR=1.26, 95% CI: 1.20; 1.32</p>

				dose-response association between the amount currently smoked and the risk of asthma 1-9 cigarettes/day: OR=1.03, 95% CI: 0.97; 1.10 10-19 cigarettes/day: OR=1.11, 95% CI: 1.04; 1.18 ≥20 cigarettes/day: OR=1.18, 95% CI: 1.11; 1.26)
Harju <i>et al.</i> [57]	2016	Hospital-based birth retrospective observational birth cohort study including 39 306 women, delivering between 1989 and 2006	SHS exposure	risk of asthma among children when both parents smoked: OR=3.7, 95 % CI: 3.2; 4.4 risk of asthma among children whose fathers smoke and mother quit during pregnancy: OR= 2.8, 95 % CI: 2.3; 3.4
Miller <i>et al.</i> [58]	2014	Cross-sectional study	Paternal smoking	positive association between paternal smoking during puberty and asthma in children: OR=1.17, 95% CI: 0.97; 1.41
Wang <i>et al.</i> [53]	2015	Systematic review (n=25 studies)	SHS exposure	risk of hospitalization for asthma among children with asthma: OR=1.85, 95% CI: 1.20; 2.86 visits to emergency department or urgent care: OR=1.66, 95% CI: 1.02; 2.69 increased risk of wheezing: OR=1.32, 95% CI: 1.24; 1.41
Bayly <i>et al.</i> [59]	2019	school-based cross-sectional survey including 11 830 children (aged 11-17 years)	SHS exposure to e-cigarettes	positive association between SHS exposure to e-cigarettes and asthma attack in the past 12 months: OR=1.27, 95% CI: 1.11; 1.47
Alnajem <i>et al.</i> [60]	2020	school-based cross-sectional enrolling high school students (n=1565, aged 16-19 years)	SHS exposure to e-cigarettes	positive association between exposure to household SHS to e-cigarettes: current asthma: PR = 1.56, 95% CI: 1.13; 2.16 current uncontrolled asthma symptoms: PR = 1.88, 95% CI: 1.35; 2.62

Abbreviation: SHS, second-hand smoke

Epidemiological evidence suggests that the effects of maternal smoking are heritable with further generations continuing to present poor respiratory outcomes, probably through epigenetic mechanisms [51, 52]. According to these studies, grandmaternal smoking has been shown to increase the risk of a grandchild's asthma independently of maternal smoking. Furthermore, exposure to tobacco smoke is also associated with more severe asthma symptoms, increased risk of asthma exacerbations and hospitalizations [53]. A systematic review showed an approximately 2-fold increase in the risk of hospitalization for asthma among children with asthma and exposed to SHS than children with asthma but without SHS exposure [53]. Exposure to SHS was also significantly associated with visits to the emergency department or urgent care and with an increased risk of wheezing [53].

Since the early 2000s, electronic cigarettes (e-cigarettes) have been marketed worldwide as a “safer” electronic alternative to combustible cigarettes and as a device likely to help stop smoking [54]. Unlike a cigarette, e-cigarettes produce a respirable aerosol without burning tobacco. Although the number of studies on the short- and long-term health effects of e-cigarettes is very limited, recent studies suggested that exposure to e-cigarettes is also a significant factor that has been shown to increase the incidence of asthma [55]. In 2019, 33% of the youth with asthma who reported having an asthma attack in the previous year were exposed to SHS to e-cigarettes [54].

Overall, the evidence contributes to a growing understanding about the timing of SHS exposure and the development of childhood asthma, showing that knowledge of critical time windows of exposure is important in implementing targeted interventions.

3. Mechanistic insights into air pollution exposure and the pathogenesis of asthma

Children seem to be particularly vulnerable to adverse effects of air pollution because of their relative respiratory and immune system immaturity. Although several mechanisms underlying the association between exposure to air pollutants and childhood asthma that involve environmental epigenetic regulations, such as DNA methylation, oxidative stress, and damage, disrupted barrier integrity, inflammatory pathways, and immunological responses, and enhancement of respiratory sensitization to aeroallergens have been described, the mechanistic basis of air pollution effects on asthma remains elusive.

Exposure to air pollutants has been associated with the production of reactive oxygen species (ROS) and consequently induces epithelial cell inflammation, airway hyperreactivity, tight junction barrier permeability and lung injury [61, 62]. Exposure to

O₃ and SO₂ may affect the production of cytokines in airway epithelial cells, which promote Th2 phenotypic differentiation and the production of IgE [63]. Furthermore, DNA methylation of NOS genes may also be an important epigenetic mechanism that potentially modulates TRAP-induced inflammatory responses. Exposure to TRAP has been associated with higher levels of exhaled nitric oxide (NO) and lower levels of DNA methylation in the promoter regions of the NOS3 gene at various lag periods in children with asthma living in a seaport-adjacent community with a high density of diesel truck traffic [64]. The associations of BC exposure with demethylation of *IL4* and *NOS2A*, lowering *IL4* and inducing nitric oxide synthase encoded by *NOS2A* and therefore exhaled NO levels appear to be stronger among the atopic compared with the nonatopic children [65].

DEP exposure produces reactive oxygen species in the lungs and the oxidative stress-induced can lead to sensory nerves stimulation responsible for reflex events and common respiratory symptoms, such as coughing and wheezing. PAHs, major constituents of DEP can directly activate airway C-fiber afferents and activation of the transient receptor potential ankyrin 1 (TRPA1) ion channel expressed on airway afferents through activation of AhR and subsequent mitochondrial ROS production, which is known to activate TRPA1 on nociceptive C-fibers [66].

Ozone exposure results in the accumulation of ROS most likely through lipid peroxidation processes of the pulmonary surfactant phospholipids and cell membranes. ROS in turn rapidly activates the release of alarmins leading to a cascade of pro-inflammatory changes in structural and immune cells in the respiratory mucosal tissue [67]. PM exposure has also been shown to disrupt epithelial tight junctions in a dose-dependent manner [68] therefore facilitating aeroallergen uptake and therefore promoting allergic sensitization. This hypothetical mechanism would also support a time lag between early childhood structural and functional changes in growing lungs with subsequent expression of asthma symptoms at an age when asthma can be distinctly identified.

3.1. Cleaning and consumer products

Exposure to cleaning and consumer products may damage the respiratory epithelium, causing bronchial hyperresponsiveness and affecting inflammatory pathways of the innate immune system [69]. According to Wang *et al.* [70] cleaning products may also disrupt the functionality of the bronchial epithelium, even in dilute concentrations. Most cleaning products can induce sensitization by an immunologic mechanism, increasing bronchial hyperreactivity to allergens to which the individual has been previously sensitized [71]. Studies on exposure to swimming pool environments suggested that

chlorination products may promote allergic sensitisation by compromising the permeability or the immunoregulatory function of epithelial barriers [71]. Hox *et al.* [72] in an animal model suggested that bronchial hyperreactivity due to exposure to hypochlorite may depend on a neuroimmune interaction involving TRPA-1-dependent stimulation of sensory neurons and mast cell activation. Disinfectants may also change the composition and diversity of children's microbiome, which has been linked to an increased risk of developing childhood asthma.

3.2. Tobacco and e-cigarettes exposure

Exposure to tobacco has been associated with oxidative imbalance and stress, which may change the barrier function of the epithelial layer by reducing ciliary beating and enhancing mucus production, epithelial to mesenchymal transition, and immune dysfunction [73]. Moreover, some cigarette smoke derivatives may disrupt epithelial cellular junctions, allowing for deeper penetration of toxins and allergens [73]. Oxidative stress related to exposure to tobacco may activate the transcription of factors involved in inflammatory responses, which are responsible for sustained immune cell recruitment and activation. Furthermore, prolonged exposure to tobacco may enhance both Th2- and Th1-mediated inflammatory responses, being associated with a more severe asthma phenotype [74]. In utero exposure to nicotine may affect lung development in the fetus, consequently leading to impaired lung function and an increased risk of asthma [75]. Nicotine has been also associated with epigenetic changes, such as DNA methylation or changed microRNA expression, which may modulate epithelial differentiation, immune cell differentiation, or both, in a permanent way [76].

The chemical compounds, including reactive carbonyls, resulting from heating in e-cigarettes are also known for their toxic and irritant effect on the airways, causing airway constriction, direct damage to airway epithelium, and changes in gene expression [77]. Similar to exposure to cigarettes, acute exposure to SHS in e-cigarettes was also associated with altered lung cells, including the small airway epithelium, alveolar macrophages, and circulating endothelial microparticles [78].

4. Prevention and mitigation of the effects of air pollution on childhood asthma

Actions against the well-known childhood asthma risk factors, industrial activities, TRAP, cleaning and consumer products, and smoking, should be taken simultaneously. Global, national, local, and individual action plans should be implemented considering each

situation and need to be planned and implemented by engaging policymakers, governments, civil society, and each individual (**Figure 3**).

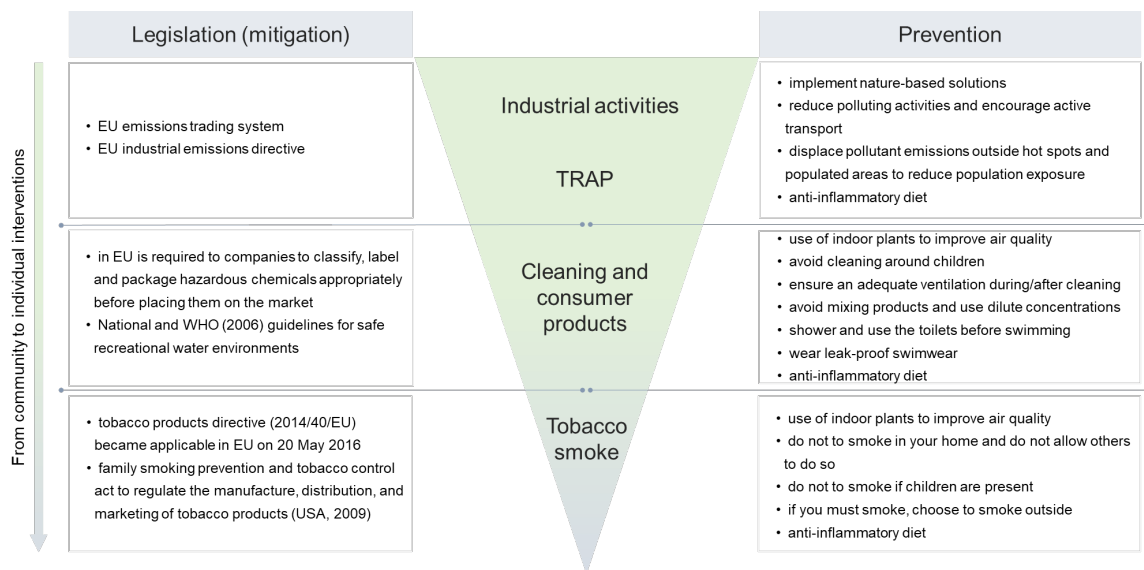


Figure 3. An action plan toolbox to prevent and mitigate air pollution effects on childhood asthma

4.1. Industrial activities and traffic-related air pollution

The design of sustainable cities and the evolution of environmental conditions are two of the main future challenges to strengthen urban resilience and sustainably. One promising approach to achieve these challenges is to implement nature-based solutions (NBS) in the management and design of urban areas. NBS can provide several benefits to cities and address different societal challenges, including air pollution, while also contributing to restoring biodiversity, improving human health, and thus supporting community wellbeing and livelihoods. NBS, including indoor plants in living rooms and workplaces, trees in streets and parks, green roofs and green walls, urban forests, and green infrastructures, could be effectively implemented as an economic and sustainable solution to reduce exposure to air pollution. Pollutants may be removed from the atmosphere through wet and dry deposition on the tree surface as in the case of particles, and/or by stomatal adsorption and absorption processes in the case of gaseous pollutants. The identification of specific plant species based on their air pollution tolerance index, physiological characteristics, and habitat may be helpful in the mitigation of air pollutants from different to a greater extent. The BRIDGE project demonstrated that increasing canopy cover between 20% and 30% could improve PM10 removal to a range of 3% by the year 2050 (www.bridge-fp7.eu). Recently, and within the framework of the GreenInUrbs project, the “*Specifind*” tool has been developed to support NBS by

allowing for the selection of the best tree species based on several parameters, including the improvement of air quality (http://www.greeninurbs.com/p_specifind/).

The European Union (EU) has been making efforts to reduce pollutant emissions from industrial sources, mostly by applying legal regulations, such as the EU Emissions Trading System and the Industrial Emissions Directive [79, 80]. Data submitted to the Convention on Long-range Transboundary Air Pollution by the associated Nations, and published by the European Environment Agency (EEA), show that the concentrations of industrial emissions have been tendentially decreasing since 1990 (**Figure 4**), suggesting that these regulations can indeed be potential solutions to mitigate the effects of industrial pollution [81].

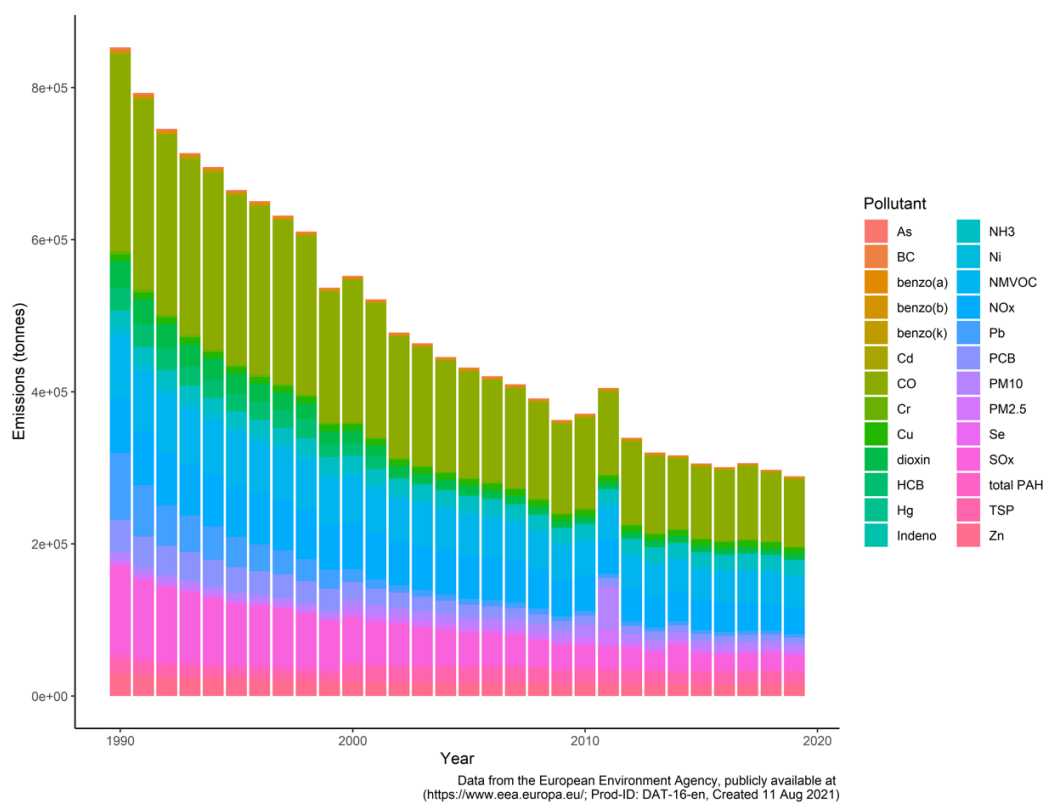


Figure 4. Industrial emissions in the EU (1990-2019)

However, according to the EEA, industrial pollution and greenhouse gases are estimated to have costed society between 277 and 433 billion euros in 2017, revealing that despite the efforts from the European Green Deal and the Zero Pollution Action Plan, more needs to be done to reduce the impact of industrial emissions [82]. To tackle industrial pollution, the EU has been developing a set of policies that would support the twin green and digital transitions to a low-carbon industry [83]. However, since these policies were published in March 2020, they were rapidly subjected to the constraints of the COVID-19 pandemic, which changed the industrial sectors worldwide.

The introduction of low-emission zones (LEZ) in urban areas has also been associated with improvements in urban air quality and has been defined to meet legislative limits and deliver improvements to childhood respiratory health, including asthma symptoms. Providing and maintaining cost-effective and easier alternatives, including expanded public transport systems, car share, safe cycles, and walkable networks, to move through the urban environment may also reduce fuel consumption and, in turn, air pollution through reduced exhaust emissions. It should also be recognized the role of diet to modulate the effects of air pollution on asthma [84]. An anti-inflammatory diet characterized by higher consumption of fruits, vegetables, and legumes, fatty fish and whole grains, may also decrease the exposure effect of PM_{2.5} and PM₁₀ on childhood asthma [84].

4.2. Cleaning and consumer products

Cleaning products contain innumerable irritating and sensitizing chemical compounds, which are often undisclosed making it difficult to protect consumers. Given the growing evidence, the American Lung Association recommended the use of products that do not contain or have reduced concentrations of VOCs, fragrances, irritants, and flammable ingredients. Although some countries, such as Canada and the United States of America, are not required to list all the chemical substances and mixtures in consumer and cleaning products, in EU is required companies to classify, label and package hazardous chemicals appropriately before placing them on the market. To minimize exposure when cleaning and consumer products do need to be used, parents/caregivers should avoid cleaning around children, ensure adequate ventilation of indoor spaces during and after cleaning activities, avoid mixing products and use diluted concentrations.

4.3. Tobacco and e-cigarettes exposure

Reducing children's exposure to ETS is essential: do not smoke at home and do not allow others to do so. If you must smoke, choose to smoke outside.

5. Conclusions

Environmental conditions, such as air pollution, are a major determinant of childhood asthma, but such conditions are not shared equally across the population, regions, and settings where people live, work, and spend their time. Urban areas may be affected by industrial activities and traffic-related emissions with high levels of air pollution and a lack

of quality and safety features that enhance healthy living, such as urban natural spaces. Urban conditions and air quality are not only important features for national and local authorities to shape healthy cities and protect their citizens from environmental and health risks, but they also provide opportunities to mitigate inequalities in the most deprived areas where the environmental burden is highest. Actions to avoid exposure to indoor and outdoor air pollutants should be complementary at different levels –*individual, local, and national levels*– to take strong measures to protect children who have little or no control over the air they breathe.

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