

# Urban-level environmental factors related to pediatric asthma

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## Abstract

During the 20th century, urbanization has increasing and represented a major demographic and environmental change in developed countries. This ever-changing urban environment has an impact on disease patterns and prevalence, namely on noncommunicable diseases, such as asthma and allergy, and poses many challenges to understand the relationship between the changing urban environment and the children health. The complex interaction between human beings and urbanization is dependent not only on individual determinants such as sex, age, social or economic resources, and lifestyles and behaviors, but also on environment, including air pollution, indoors and outdoors, land use, biodiversity, and handiness of green areas. Therefore, the assessment and identification of the impact of urban environment on children's health have become a priority and many recent studies have been conducted with the goal of better understanding the impacts related to urbanization, characterizing indoor air exposure, identifying types of neighborhoods, or characteristics of neighborhoods that promote health benefits. Thus, this review focuses on the role of urban environmental factors on pediatric asthma.

**Keywords:** asthma, biodiversity, children, endocrine-disrupting chemicals, environment, microbiome, urbanization

## Introduction

According to the Organization for Economic Co-operation and Development the impact of environmental risk factors on health are diverse and complex in both severity and clinical significance.<sup>1</sup> The World Health Organization (WHO) reported that 24% of the global burden of disease and 23% of all deaths are attributable to environmental factors, being their effects not equally distributed across all age groups.<sup>2</sup> The European Union Environment and Health Action Plan (EHAP) also highlights the concern about the effects of environmental determinants on human health, including respiratory diseases, asthma and allergies, particularly those affecting vulnerable groups such as children.<sup>3</sup>

The most recent estimate, from the Global Burden of Disease Study 2015, stated that there are more than 300 million people with asthma worldwide, and there may be an additional 100 million people with asthma by 2025, making it one of the most common noncommunicable disease.<sup>4</sup> Although the prevalence of asthma is higher in developed western countries, the disease is recognized worldwide. In developing countries, the prevalence of

asthma tends to be  $\leq 1\%$ , much lower than the 10% usually found in developed western countries.<sup>5</sup> Within populations, and considering their level of development, the prevalence of asthma follows an urban-rural gradient.<sup>6,7</sup> In children, according to the International Study of Asthma and Allergies in Childhood performed in several countries, this prevalence has also increased in many countries that are experiencing rapid increases in urbanization and westernization of lifestyle.<sup>8</sup> The differences in prevalence in most regions suggest that the factors that affect asthma vary between locations.<sup>8</sup> These factors may act differently in developed countries and in developing countries, and their interaction with lifestyles may also be important. There are likely to be several of environmental factors associated with the development process related to the global changes, including loss of protective factors, which may be associated with differences between regions.<sup>9</sup> In addition, the cause of this increase in asthma prevalence that began in the late 1970s<sup>5</sup> is still unclear, but it is consistent with a rise in other allergic diseases, such as rhinitis and atopic dermatitis, and autoimmune diseases: type 1 diabetes, multiple sclerosis, and Crohn disease.<sup>10</sup> Concomitantly, there has been a decrease in the incidence of many infectious diseases in developed countries as a result of improved health and socioeconomic conditions.<sup>10</sup> These trends cannot be explained only by genetic reasons, but by an interaction between multiple genetic and environmental factors.<sup>11</sup>

Environmental factors, including outdoor and indoor air exposures, have been associated not only with asthma development but also with its exacerbation.<sup>12,13</sup> It is widely acknowledged that exposure to outdoor air pollutants, including ozone (O<sub>3</sub>), nitrogen dioxide (NO<sub>2</sub>), sulfur dioxide (SO<sub>2</sub>), and particulate matter (PM), can increase the risk of developing asthma.<sup>14,15</sup> In fact, guidelines recommend that individuals with asthma should avoid outdoors when concentrations of pollutants are elevated, as they are related with asthma exacerbations, increased symptoms, and with a greater risk of hospitalization among children with asthma.<sup>14</sup> A growing body of evidence also shows that chronic exposure to traffic-related pollution, even at

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low levels within current standards, impairs lung function in childhood and increases the risk of clinically significant decreases in lung function.<sup>16–18</sup> Children living in neighborhoods whose air quality improved during the observation period had a more pronounced trajectories of lung function growth than those living in neighborhoods whose air quality did not improve.<sup>17</sup> Indoor environments also represent an important contribution of the children's environmental exposure due to the time that they spend indoors, the higher concentration of several pollutants indoors, and to the risk related to specific environmental factors associated with asthma and asthma-related symptoms, including chemical compounds as endocrine disruptors.<sup>14,19</sup>

This review focuses on the role of urban environmental factors on pediatric asthma considering 2 interactive levels—the indoor environment and neighborhood. First, the role of indoor exposure, including exposure to endocrine-disrupting chemicals, on asthma and on human microbiome is described. Then, key determinants of neighborhood environment, such as urbanization, biodiversity, walkability, and air pollution in urban environment, are highlighted as playing an important role in human health.

### *Indoor air quality*

Most people are aware that outdoor air pollution can impact their health, but the less recognized, or even unsuspected, indoor air pollution can also have significant and harmful health effects. The Scientific Committee on Health and Environmental Risks reported that indoor air pollution is the 8th most important risk factor for disease, responsible for an estimated 2.7% of the global burden of disease. Estimates also show that 1.5 to 2 million deaths every year could be attributed to indoor air pollution.<sup>20</sup>

According to the US Environmental Protection Agency indoor levels of pollutants may be 2 to 5 times, and occasionally more than 100 times, higher than outdoor levels.<sup>21</sup> The levels of indoor air pollutants are of particular concern because most people spend approximately 90% of their time indoors, at home, school, workplaces, transportation vehicles, or at indoor recreational places,<sup>22,23</sup> having a significant impact on individuals' health and quality of life.<sup>24,25</sup> Indoor environments represent a mixture of (a) outdoor pollutants, associated to traffic and industrial activities, which can penetrate the building envelope through infiltrations or ventilation specific openings (windows or other) or mechanical and (b) indoor pollutants, resulting from emissions from building materials, furnishings, cleaning products, heating and cooling systems, humidification devices, moisture processes, electronic equipment, pets, combustion sources (such as burning fuels, coal, wood, incense, and candles), and also from the behaviors of occupants (smoking, painting, etc).<sup>24,26</sup>

Increasing urbanization, changing behaviors and use of materials and consumer products are also associated to qualitative and quantitative variations of indoor air quality (IAQ) over the years, underlining an increase in some critical pollutants and their concentrations.<sup>26</sup> IAQ can be impaired by several chemicals, including carbon monoxide (CO), O<sub>3</sub>, nitrogen oxides (NO, NO<sub>2</sub>), radon, volatile organic compounds (VOCs), PM and fibers, and by biological agents, such as bacteria, fungi, and allergens.<sup>20</sup> Some of these indoor pollutants may be mainly influenced by their outdoor concentrations, have primarily indoor sources, or are influenced by both indoor and outdoor sources.<sup>26</sup> Most air pollutants found indoors are broadly similar to those found outdoors, with similar biological mechanisms for impacting on human health.<sup>27</sup> The effects of exposure to indoor air pollution may, however, be greater than those related to outdoor air, namely to vulnerable groups such as

children, young adults, the elderly, or those suffering chronic respiratory and/or cardiovascular diseases.<sup>28,29</sup> As aforementioned, children are one of the most susceptible groups, due to their physical characteristics,<sup>30,31</sup> as well as the time spent indoors. This biological mechanism in the past decades, many studies have focused on the effect of indoor air pollutants on children health, including asthma and allergies. In 2000, the Committee on the Assessment of Asthma and Indoor Air of the Institute of Medicine reviewed and summarized the evidence for associations between indoor air exposures, namely to biological and chemical stressors, and the exacerbation and development of asthma.<sup>32</sup> More recently, Kanchongkittiphon et al<sup>33</sup> reviewed published articles on indoor exposures and exacerbation of asthma. Exposure to house dust mite allergens was associated with dust mite sensitization, which was in turn associated with asthma; the protease activity of house dust mite may act on airway epithelial cells and on the activation of protease-activated receptor-2 triggering an innate immune response and the release of proinflammatory cytokines, such as interleukin-6 (IL-6) and IL-8 from airway epithelial cells.<sup>34</sup> Kanchongkittiphon et al<sup>33</sup> also reported that exposure to chemical pollutants, such as formaldehyde, 2-ethyl-1-hexanol, and di(2-ethylhexyl) phthalate, was found to be associated with asthma development and airway inflammation in children. In line with previous studies, Patelarou et al<sup>35</sup> stated that most of the individual VOC appeared to be significant risk factors for asthma with the highest odds ratio (OR) for benzene [aOR = 2.92; 95% confidence interval (CI) 2.25; 3.80] followed by ethylbenzene (adjusted OR (aOR) = 2.54; 95% CI 1.16; 5.57) and toluene (aOR = 1.84; 95% CI 1.41; 2.41).

Among different indoor environments, schools, besides their homes, are one of the most important settings for children, since they spend at least one-third of their time in schools. According to Oliveira et al<sup>36</sup> Portuguese children spend per day up to 10 hours of their time at school, mainly in classrooms, demonstrating the relevance of understanding the health effects of indoor air pollutants in this environment. Schools are also indoor settings with a high population density, in which different pollutants may remain for a long time due to insufficient ventilation and existence of indoor sources, and are often characterized by infrequent interventions and building maintenance.<sup>37,38</sup> Therefore, characterization of indoor air pollution in school environments is of critical public health concern given the potential long-term adverse consequences from such exposures. Associations have been found between wheezing and high exposure to indoor formaldehyde, pinene, PM (PM<sub>2.5</sub> and PM<sub>10</sub>), and CO in classrooms.<sup>39</sup> In addition, children exposed to high benzene<sup>39</sup> and PM<sub>10</sub> levels<sup>40</sup> were more likely to have nocturnal cough. Similar associations were observed between exposure to formaldehyde, VOC, and PM<sub>2.5</sub> and asthma.<sup>38</sup> Fsadni et al<sup>39</sup> reported that school IAQ is dependent on the school building and classroom characteristics and cleaning/maintenance schedules, and that exposure to several indoor air pollutants was associated with upper and lower airway inflammation. Recently, studies related to IAQ in schools in different European countries have showed that children who study and live in industrial areas have an increased risk of respiratory symptoms when compared to those living in other areas.<sup>41,42</sup> Although the presence of moulds in schools was also associated to adverse health effects such as asthma symptoms, coughing, wheezing, and upper respiratory symptoms,<sup>43</sup> Cavaleiro Rufo et al<sup>44</sup> reported that classrooms with increased diversity scores showed a significantly lower prevalence of children with atopic sensitization. Among school indoor air pollutants, VOC could be a significant group of compounds<sup>45,46</sup> since they are largely present indoors and can be

released continuously and slowly over a long time, thus posing a higher risk to human health.<sup>47</sup> In 2017, Zhong et al<sup>46</sup> reported higher concentrations of aromatic (toluene, ethylbenzene, xylene, 1,2,4-trimethylbenzene), alkanes (n-heptane, n-undecane, n-hexadecane), and terpenes volatile compounds (pinene and limonene) in classrooms, suggesting the presence of indoor sources, including air fresheners, adhesives, glues, paints, sprays; renovation activities and painting of walls; and wood products (furniture, parquet), personal care, and cleansing products, respectively.<sup>48</sup> On the contrary, the specific VOC to which occupants are exposed nowadays are substantially different from those that occupants experienced 50 years ago,<sup>26</sup> suggesting changes in type and concentration from day-to-day, month-to-month, year-to-year, and decade-to-decade. Some VOC measured in schools have been associated with a variety of health effects and symptoms such as asthma and allergies.<sup>49,50</sup> The Children's Environment and Health Action Plan for Europe of WHO found a negative association between maximal expiratory flow at 75% of vital capacity (MEF<sub>75</sub>) and formaldehyde, benzyl-butyl-phthalate, and the sum of polybrominated diphenyl ethers. Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV<sub>1</sub>) were also negatively associated with ethylbenzene, xylenes, and tris(1,3-dichloro-2-propyl)-phosphate.<sup>51</sup> Beginning in the 1970s, other chemical compounds, including brominated and organophosphate flame retardants and plasticizers, have been added to consumer products, including furniture, children's products, and electronics.<sup>52</sup> Recent studies have linked the exposure to high concentrations of these compounds in indoor dust to higher prevalence of asthma (OR=5.34, 95% CI 1.45; 19.7) and allergic rhinitis (OR=2.55, 95% CI 1.29; 45.0).<sup>53</sup> According to Scientific Committee on Health and Environmental Risks, in infants and children, exposure to VOC increases the risk of respiratory and allergic conditions, such as asthma, wheezing, chronic bronchitis, reduced lung function, atopy and severity of sensitization, rhinitis, and respiratory infections.<sup>20</sup> In addition, in a national representative cross-sectional study in France, high concentrations of VOC in homes were associated with an increasing prevalence of asthma and rhinitis in adults.<sup>20</sup> Several studies have also demonstrated that the role of VOC in the development and exacerbation of asthma and allergic disease,<sup>54,55</sup> suggesting that VOC exposure can influence the immune responses, increasing Th2 polarization.

Although exposure to ubiquitous environmental pollutants has increased in recent years and the impact of these pollutants on human health have been widely explored, less attention has been paid to the potential health risks of exposure to VOC functioning as endocrine-disrupting compounds (EDCs).<sup>56</sup> Indoor exposures to suspected endocrine disruptors have markedly increased<sup>26</sup> and many of these compounds may be absorbed by other indoor surfaces after being released to the air and continue to be desorbed long after the host material is removed.<sup>26</sup> Therefore, research on EDCs should focus on understanding factors influencing its indoor air concentrations and the effect of their exposure on human health, especially in children. Beyond chemical screening programs to identify chemicals with endocrine-disrupting activity, many questions remain about the way to assess implications of this exposure on health outcomes.

### Endocrine-disrupting compounds

EDCs have been described following the discovery of the effects of the insecticide dichloro-diphenyl-trichloroethane on workers in cotton fields.<sup>57</sup> According to Bouchard,<sup>57</sup> in 1962, Rachel Carson

in "Silent Spring," describes a world where there is no more bird singing, because they have been eradicated by the environmental toxics. However, it was in the medical field that their mechanism of action was discovered: children of women who received diethylstilboestrol, while they were pregnant, presented genital malformations, infertility, and clear cell adenocarcinomas of the vagina. In addition, the second generation presented a high rate of hypospadias in boys.<sup>57</sup> In 2002, the International Programme on Chemical Safety defined EDCs as "*an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations.*"<sup>58</sup>

Some chemicals used in building materials, furnishings, and consumer products have been shown to be EDCs,<sup>59</sup> making them potentially important indoor contaminants/pollutants and suggesting that indoor exposure may be a greater contributor to overall EDCs exposure.<sup>59,60</sup> Most of EDCs are synthetic organic chemicals used in a wide range of materials and goods and can be found indoors in wide variety of products, including building and furnishing materials, pesticides, along with cleaning products.<sup>61-63</sup> In addition to the time spent indoors, where EDCs concentrations can be more relevant than the outdoor concentrations,<sup>38,64</sup> humans are continuously exposed to a diverse number of EDCs not only through inhalation of air and particles, but also by contact with contaminated media (soil or surfaces), consumption of food and drinking water, and through direct dermal contact (eg, cosmetic products).<sup>63</sup> Ingestion of contaminated food and beverages have been pointed as the major pathways of exposure to EDCs.<sup>65</sup> Yang et al<sup>65</sup> reported that some EDCs, including bisphenol A, may be leached from the lining of food and beverage cans, where it is used as an ingredient in the plastic used to protect the food from direct contact with the can. Furthermore, current data suggest that there is a chronic and sustained exposure to indoor EDCs through inhalation.<sup>66-68</sup>

Although the development of synthetic chemical compounds has improved our daily life, the role of environmental chemicals in human health has increased in past years, suggesting that the effect of environmental exposure could constitute the paradox of progress,<sup>69</sup> with EDCs exposure implicated in the development of several human diseases.<sup>70,71</sup> Over recent decades, several studies recognized that EDCs can disturb many hormonal pathways, such as altered reproductive function in men and women, increased incidence of breast cancer, abnormal growth patterns, and neurodevelopmental delays in children, as well as changes in immune function.<sup>72</sup> The age at which an individual is exposed to an EDCs also has implications on health effects; during early fetal and childhood development, a wide variety of genes are activated and inactivated in a sequential manner, providing numerous targets for these environmental exposures. Exposure to EDCs during childhood can induce long-lasting effects persisting throughout adulthood and affecting future generations.<sup>63</sup> Indeed, it is now clear that exposure to EDCs during early development results in different health effects than exposures during adulthood. In general, higher concentrations of EDCs are required to cause toxicity in adults, and their effects only last as long as the EDCs are present.<sup>73</sup> Although there is growing evidence on the health effects of EDCs in adults, there is limited knowledge regarding the association between exposure to EDCs during childhood and the development of asthma and/or allergies. This underlines the need of a better understanding of the EDCs exposure processes and health outcomes in children, who may be especially susceptible to effects at low concentration, considering the increasing amount of time spent indoors.

According to the WHO, approximately 800 chemicals are known or suspected to be capable of interfering with various mechanisms of the endocrine system, such as receptor binding and/or hormone synthesis, potentially inducing adverse health effects in exposed individuals or populations and possibly playing a substantial role in many endocrine disorders.<sup>63,71</sup> Given the widespread exposure to several EDCs, many of which with potential health effects in the general population, whether mixtures of EDCs affecting health is no longer a question limited to patients, but is of importance for all population groups, especially for children.<sup>74</sup> Furthermore, each chemical is present at a dose that may or not have an effect in the case to the EDC alone, and the mixture may have an effect.<sup>74</sup> In 2019, Yu et al<sup>75</sup> hypothesized the possibility of potential interactive effects (synergistic or antagonistic) among the multiple EDCs existing in the environmental mixture that may be not reflected by the effects resulting from exposure to the individual compounds.

For many years, the concept proposed by the Swiss physician and alchemist, Paracelsus in the 1500s that “the dose makes the poison” has been used by regulators to establish risk assessment profiles of chemicals. This concept predicts that higher doses of a chemical will cause greater harm than low doses. However, similar to hormones, even low concentrations of EDCs (from parts-per-trillion to parts-per-billion range) may have effects that are not predicted by effects at higher doses.<sup>76</sup> EDCs may also exert nontraditional dose-responses due to the dynamics of several receptor occupancy and saturation. Thus, low doses may have more impact on a target tissue than higher doses, and the effects may be entirely different.<sup>76–78</sup> This nonmonotonic dose responses may be due to different mechanisms, such as opposing effects induced by multiple receptors differing in their affinity, receptor desensitization, negative feedback with increasing doses, or dose-dependent metabolism modulation.<sup>79</sup> The nonmonotonic dose responses have been reported in several human studies, suggesting that the risk of diseases does not increase with an increasing level, but often tends to plateau or even decrease with increasing levels.<sup>80</sup> In addition, the need to consider mixture effects when assessing the risks associated with EDCs exposure has been widely recognized,<sup>81</sup> since these compounds can be released as mixtures and interact within or between classes.<sup>77,78</sup>

Initially, it was suggested that EDCs act through nuclear hormone receptors, including estrogen and androgen receptors, progesterone receptors, and thyroid receptors, among others.<sup>78</sup> Indeed, some recent studies have showed that EDCs are capable of acting through nonsteroid receptors, transcriptional coactivators, enzymatic pathways involved in steroid biosynthesis and/or metabolism,<sup>78,82</sup> have a direct effect on genes<sup>83</sup> and an epigenetic impact,<sup>84</sup> and may also target different organs and systems.<sup>85</sup> In addition, exposure to EDCs may change cytokine production, Th1 and Th2 balance, and activate the immune system.<sup>56,86</sup> Kuo et al<sup>87</sup> showed that human bronchial epithelial cells treated with different EDCs increased bronchial smooth-muscle cell proliferation and migration by increasing the secretion of chemokines (IL-8 and RANTES), suggesting a possible role for EDCs in asthma airway remodeling. These pollutants may also induce oxidative stress and epithelial damage to initiate or augment airway inflammation and reduce inhibitory T<sub>reg</sub> function.<sup>88</sup> Furthermore, EDCs may mediate epigenetic changes through alterations in DNA methylation, which are proposed to play a role in the development of asthma.<sup>89</sup> Exposure to higher EDCs levels is related to lower methylation of TNF $\alpha$  5' CGI, which is associated with airway inflammation, hyper-responsiveness, the regulation of immune cells and a higher risk

of asthma in children.<sup>89</sup> Similar to other air pollutants that have an irritant effect, EDCs may also stimulate airway C-fiber sensory nerves, which express transient receptor potential cation channels; when exposed to irritants, transient receptor potential channels release neuropeptides locally, resulting in cough, airway irritation, mucous secretion, and bronchoconstriction mediated by the efferent pathways of the autonomic nervous system.<sup>90,91</sup> Nassi et al<sup>92</sup> and Cantero-Recasens et al<sup>93</sup> reported the role of activation and/or increased expression of transient receptor potential vanilloid 1 and ankyrin 1 channels in the pathogenesis of asthma, providing evidence for the role of ANS in the regulation of airway function.

### ***Endocrine-disrupting chemicals and development of asthma***

The focus of the effects of exposure to EDCs has earlier been on reproductive parameters and potential carcinogenic effects, but it has been recognized that different human systems can also be affected. Some researchers have suggested that exposure to EDCs, such as phthalates and bisphenol A, may contribute to the development of asthma in children. Two independent studies conducted in Sweden<sup>94</sup> and in Bulgaria<sup>95</sup> reported a statistically significant association between the concentration in house dust of di-2-ethylhexyl phthalate and allergic and respiratory symptoms in children. In Swedish homes, association between benzyl butyl phthalate in house dust and allergic symptoms was also found.<sup>94</sup> In addition, a systematic review found a positive association between PVC surface materials at home and the risk of asthma (OR=1.55, 95% CI 1.18; 2.05) and allergies (OR=1.32, 95% CI 1.09; 1.60) in children aged up to 12 years.<sup>96</sup> Donohue et al<sup>97</sup> found an inverse association between maternal bisphenol A exposure during pregnancy and wheeze at 5 years (OR=0.7, 95% CI 0.5; 0.9); however, a positive association was found between bisphenol A concentrations at ages 3, 5, and 7 years and asthma (OR=1.5, 95% CI 1.1; 2.0; OR=1.4, 95% CI 1.0; 1.9; and OR=1.5, 95% CI 1.0; 2.1, respectively). In 2015, Gascon et al<sup>98</sup> measured bisphenol A and metabolites of low- and high-molecular-weight phthalates in urine samples collected during the first and third trimesters in pregnant women and found a higher risk of asthma at age 7 years with increased prenatal exposure to bisphenol A and high-molecular-weight phthalates.

More recently, 2 studies observed that prenatal maternal urinary concentrations of biomarkers of exposure to EDCs are associated with a higher risk of asthma in children.<sup>99,100</sup> In 2018, Buckley et al<sup>100</sup> quantified urinary phenol and phthalate biomarkers in third trimester maternal samples and found a positive association between bisphenol A (OR=3.00, 95% CI 1.36; 6.59) and 2,5-dichlorophenol (OR=3.04, 95% CI 1.38; 6.68) and asthma diagnosis among boys. An inverse association was found between wheeze in the past 12 months and low-molecular-weight phthalate metabolites (OR=0.27, 95% CI 0.13, 0.59) among girls and with benzophenone-3 among all children (OR=0.65, 95% CI 0.44, 0.96). Furthermore, Berger et al<sup>99</sup> observed that prenatal maternal urinary concentrations of biomarkers of exposure to high-molecular-weight phthalates, particularly monocarboxyisooctyl phthalate, were associated with increased risk of asthma (OR=1.54, 95% CI 1.12; 2.12) and with lower FEV<sub>1</sub> ( $\beta$ = -0.09, 95% CI -0.15; -0.03) and FEF<sub>25%-75%</sub> ( $\beta$ = -7.06, 95% CI -11.04; -2.90) at age 7, after adjusting for additional chemical exposure and demographic characteristics. Paciência et al<sup>85</sup> also reported that exposure to EDCs in classrooms was associated with an increased risk of

asthma, as well as with an increased prevalence of nasal obstruction symptoms in the previous 3 months in school-children. The authors<sup>85</sup> showed that exposure to individual or combined EDCs was associated with a change in autonomic nervous system activity, suggesting that EDCs may increase parasympathetic activity, resulting in a subsequent increase in the risk of asthma and obesity.

### Chemical compounds and human microbiome

More than 100 trillion symbiotic microorganisms live on and within human beings, which together form the microbiota, playing an important role in human health and disease.<sup>101</sup> The microbial colonization process of human body begins at birth.<sup>102</sup> After birth, human microbiome composition is characterized by a succession of microbial diversity, which is affected by life events including birth gestational date, type of delivery, and by diet including feeding habits and methods (eg, breast or bottle feeding).<sup>103</sup> Infancy is a period of rapid colonization by microbial consortia that can shift in response to several events, including illness, changes in diet, and environmental exposures.<sup>102</sup> From birth, the microbial diversity increases and converges toward an adult-like microbiome by the end of the first 3 to 5 years of life.<sup>103</sup> Although the composition of an adult microbiome remains relatively stable, the combination of multiple individual-specific factors, both endogenous (genetics, life stage, health status) and exogenous (diet, lifestyle, use of antibiotics, and environmental exposures) shapes the microbiome, making every individual microbially unique.<sup>104,105</sup>

Recently, several studies reported that exposure to some environmental chemicals can also disturb the human microbiome or, conversely, that the microbiome can play a role in the development of chemical toxicity, leading to adverse health outcomes.<sup>106–108</sup> Authors identified 2 different types of interactions between chemicals and microbiome: (a) microbiome can directly metabolize some environmental chemical after ingestion or after their conjugation by the liver and (b) environmental chemicals can interfere with composition and/or metabolic activity of the human microbiome, which may affect the activity of endogenous metabolites or the toxicity of other chemicals that depend on microbiome for their metabolism.<sup>104,106,108</sup> Claus et al<sup>104</sup> described the effect of some chemicals, including pesticides, metals, persistent organic pollutants and artificial sweeteners, on microbiome composition and metabolic activity of gut microbes, suggesting that chemicals may change the community composition and function of a microbiome, but also might alter chemical exposure by damaging the metabolic capacity of the microbiome or changing the environment that supports microbiome-induced chemical metabolism. For example, chronic exposure to low doses of chlorpyrifos, an organophosphate insecticide commonly used to treat fruit and vegetable crops and vineyards, induced gut dysbiosis—a change in the microbial community structure, being associated with proliferation of *Bacteroides* sp and decreased levels of *Lactobacillus* sp and *Bifidobacterium* sp. Furthermore, exposure to persistent organic pollutants has a major impact on the host-microbiome metabolic axis, through the activation of aryl hydrocarbon receptor signaling, and also in the decrease of the *Firmicutes/Bacteroidetes* ratio.<sup>104</sup> In addition, Rosenfeld<sup>109</sup> suggested that changes in hormone production induced by exposure to environmental chemicals, such as bisphenol A, can influence the gut microbiome composition. Exposure to disinfection by-products has also been linked to changes in

composition and activity of gut microbiome.<sup>110,111</sup> Evidence from mouse studies suggest that ingested disinfection by-products were associated with elevated relative abundance of *Bacteroidetes* and dose-dependent changes in the ratio of *Firmicutes/Bacteroidetes*<sup>110</sup> and decreased levels of *Clostridium perfringens*, *C difficile*, *Enterobacteriaceae*, and *Staphylococcus*.<sup>111</sup> However, there are no studies about the dose-response relationship, namely on how the microbiome is changed by chemical dose changes, and also on how the dose-response relationship of microbiome perturbations is related to the dose of the ultimate manifestation of toxicity,<sup>107</sup> with no clear patterns on whether certain bacteria are especially vulnerable to a range of chemical exposures.<sup>109</sup> However, a specific or a mixture of chemical compounds, its dose, the moment, and duration of exposure are likely factors inducing different microbiome effects and the ability to recover after elimination of the exposure.<sup>109</sup>

Several of the above studies reported the effect of exposure to environmental chemicals by ingestion on the gut microbiome.<sup>110,111</sup> Nevertheless, exposure to such chemicals is also likely to occur through other routes, including inhalation and dermal contact, being expected that these routes of exposure may also result in relevant human microbiome changes. Disruptions in the microbiome can in turn induce effects on host physiological responses and health.<sup>101,112</sup> Thus, going forward is essential to understand the interaction between environmental exposures and microbiome, and consequent the impact on human health. Given the relevance of the microbiome to human health, persistent exposure to chemical compounds may be an unrecognized risk factor for dysbiosis, which has now been linked to several chronic noncommunicable diseases. Although effects may be subtle, children are expected to be more susceptible to ecological disturbance, given that the microbiome is highly plastic and influenced by environmental factors during this age period<sup>109</sup> where microbiome structures appear to be more dynamic and developmental. In addition, Cho and Blaser<sup>113</sup> reported other studies showing that human microbiome is completely resilient, and that returns to the status quo ante after perturbation. Nevertheless, continued perturbations may result in the loss of recovery with implications to human health.<sup>114</sup>

### Neighborhood environment

Urban environments are diverse, dynamic, and complex playing an essential role in human health and wellbeing.<sup>115</sup> Although the features of urban living encourage rural migration, recent studies have showed that the advantages of urban life can be eroded by the adverse impacts of the urban environment, such as changes in diet patterns, sedentary lifestyle, exposure to air pollution, and loss of greenspaces.<sup>116</sup> With hasty global urbanization, there is an increasing interest in understanding how urban settings and environment affect children's health.

### Urbanization and biodiversity

Urbanization is one of the most important global change processes, with approximately 54% of the world population living in cities.<sup>117</sup> If current trends continue, by 2050 the global urban population is estimated to be 6.3 billion, nearly doubling the 3.5 billion urban dwellers in 2010.<sup>117</sup> Although the process of urbanization has important implications for changes in demographic characteristics, unplanned and rapid urbanization can also cause profound impacts on environment and on physical landscape.<sup>118</sup> These changes of landscape are induced by

residential, commercial, or industrial land development processes and by new communication infrastructures, mainly controlled by social and economic factors that exceed the local conditions.<sup>119</sup> Even under scenarios of slower urbanization rates, urban areas face several challenges, such as climate change, environmental degradation, land changes, habitat fragmentation, and loss of green areas.<sup>120</sup>

Within a context of increasing urbanization, climate change and health effects, urban greenspaces are gaining a growing interest for their role as an important element for sustainable and healthy societies in an urban context.<sup>121</sup> Greenspace can greatly contribute to the urban ecosystem through air purification by absorbing certain airborne pollutants from the atmosphere, water, and climate regulation and biodiversity, providing benefits to urban residents (recreation, social interaction and inclusion, collective empowerment, and health benefits and wellbeing), and producing economic value by increasing the quality of landscapes<sup>122</sup> and the attractiveness of the city within the context of increasing city competition.<sup>122</sup>

In addition, green areas, including forests, parks, and other natural areas, have been associated with better self-reported health and lower stress scores,<sup>123</sup> increased physical activity, and improved health.<sup>124</sup> James et al<sup>125</sup> reviewed and summarized the evidence on exposure to greenness and various health outcomes. A strong consistency was reported between greenness and physical activity, even after adjustment for a range of individual and area-level potential confounders, as well as with the lower risk of overweight or obesity. In addition, street tree density and other urban greenery have been associated with increased playtime outdoors, physical activity,<sup>125,126</sup> and lower prevalence of overweight/obesity among children.<sup>127</sup> A meta-analysis including 10 UK studies involving 1252 participants showed that physical activity in green places, even of short duration, significantly improved both self-esteem and mood.<sup>128</sup> Similar results were observed among 276 children residing in the city of Edinburgh. Findings suggested that higher use of greenspace in urban areas was positively associated with better quality of life, including friends and self-esteem subscales.<sup>129</sup> In addition, several on-going studies have examined the health effects to forests and elements of forest settings.<sup>130,131</sup> A review of field experiments conducted in 24 forests across Japan on the effects of *shinrin-yoku* (taking in the forest atmosphere or “forest bathing”) showed that forest environments could lower concentrations of cortisol, decrease heart rate and blood pressure, increase parasympathetic nerve activity, and lower sympathetic activity compared with city settings.<sup>132</sup> Park et al<sup>131</sup> reported a benefit associated with the practice of *shinrin-yoku* and nature therapy, suggesting that nature has healing and restorative properties that contribute to health and well-being. Authors reported a positive effect of *shinrin-yoku* on the immune system function, cardiovascular and respiratory system, depression and anxiety, mental relaxation, and on human feelings of gratitude and selflessness. Even research involving the use of photos of greenspaces has the same physiological effects. The nature views appeared to have a restorative effect with greater decreases toward baseline values after the stressor, induced by changes in the autonomic nervous system activity, compared to viewing built environments.<sup>133,134</sup>

Several studies from the last years have showed that exposure to greenness may also be protective of asthma and allergic diseases. Recently, Paciência et al<sup>135</sup> found that green school areas tended to be associated with higher lung volumes compared with built areas. FVC was significantly lower in in-built than in

green areas. After adjustment for age, sex, asthma, WHO *z* score for BMI and family history of asthma or allergy, the school environment explained 98% and 96% of the school effect on FVC and FEV<sub>1</sub>, respectively. In addition, the results suggest that autonomic nervous system may play a role in mediating the interaction between the environment and the individual.<sup>135</sup> Ruokolainen et al<sup>136</sup> found an inverse association between higher forest and agricultural land within 2 to 5 km around children and adolescents’ homes and the risk of atopic sensitization, especially in rural areas characterized by less densely built-up areas and more native vegetation. Among children older than 6 years, a dose-dependent relationship was observed, suggesting a causal link. In Spain, a study involving 2472 children investigated the effect of availability and accessibility of greenspace around homes in 2 biogeographical regions, Euro-Siberian and Mediterranean region, on respiratory health. Higher residential surrounding greenness and proximity to green spaces were associated with reduced risk for wheezing in Euro-Siberian, but not in Mediterranean region. In contrast, the risk of bronchitis increased with lower residential proximity to greenspaces in the Mediterranean region but no significant associations were observed in Euro-Siberian region.<sup>137</sup> Similar results were observed in 2 birth cohorts in Germany.<sup>138</sup> Fuertes et al<sup>138</sup> reported a significant difference between Normalized Difference Vegetation Index (NDVI), which provides a measure of vegetation, and allergic rhinitis among 2 distinct areas. In urban areas, NDVI in living environment was positively associated with allergic rhinitis, whereas in rural areas, greenspaces have a protective impact. A recent study developed among 49,956 New Zealand children born in 1998 and follow-up until 2016 suggested that exposure to greenness and vegetation diversity were associated with a lower risk of asthma.<sup>139</sup> An increase of home neighborhood greenspaces, measured as NDVI, across children’s life course was associated with a 6% lower risk of asthma. Vegetation diversity (total number of natural land cover types) was also associated with a decrease risk of asthma. Both early- and late-life exposures to greenness were reported to be protective factor of asthma.<sup>139</sup> Within urban areas, exposure to higher neighborhood greenness around home in early life was negatively associated with incidence of asthma during preschool years, but no association was observed in childhood (6–10 years).<sup>140</sup> However, in New York, tree canopy around the prenatal residential address has been associated with an increased risk of asthma among 7-year-old children.<sup>141</sup> Beyond cultural and lifestyle characteristics, in their study Tischer et al<sup>137</sup> reported that the type (natural or artificial) and quantity of urban greenspace, the introduction of non-native vegetation and air pollution levels may be important factors in its relation to respiratory health effects.

Furthermore, the current trend of urban growth has several environmental impacts on the surrounding ecosystems, land resources and consumption, structure, and pattern of the urban area, namely on the conversion of greenspaces into the built-up areas.<sup>142,143</sup> Urban cities tend to agglomerate, forming urban clusters or corridors, along which transportation and other forms of development occur.<sup>144</sup> As a consequence, urban greenspace has come under increasing pressure during the urbanization process and this negatively affects the structure and function of ecosystems and consequently the biodiversity and the relationships between the natural environment and human microbiome.<sup>122,143,145,146</sup> According to the biodiversity hypothesis, the reduced exposure of natural environments, and therefore microbial diversity, adversely affects the human microbiome

and may lead to the inadequate stimulation of immune regulatory circuits and clinical disease.<sup>147,148</sup> This hypothesis builds upon the “old friends” concept, which highlights the long-term evolution of humans with old infections, commensal and environmental microbiotas that have a critical immune regulatory role to play.<sup>148</sup>

Several studies reported a significant effect of living environment on the composition of human microbiome and consequently on asthma and allergic diseases.<sup>146,149–151</sup> The border between Finland and Russia marks one of the sharpest boundaries between living standards, environment exposure, and health. In Russian Karelia, people have small houses in the countryside with some cattle and domestic animals and produce much of their own food in small gardens. In contrast, Finnish Karelia has experienced major economic growth and rapid urbanization. Although the 2 current populations share partly the same ancestry, with approximately 15% of the current population of the Karelian Republic are Finns or Karelians, and the similar geoclimatic and vegetative conditions, the prevalence of asthma, hay fever, and positive allergen-specific IgE levels to birch pollen, were significantly higher among children and young adolescents in Finnish than in Russian Karelia (8.8 vs 1.6; 15.6 vs 1.1; and 42.8 vs 15.7, respectively).<sup>149,152</sup> Adults cohort showed that among those born after 1940s, sensitization to birch pollen increased in Finnish Karelia.<sup>152</sup> Furthermore, randomly selected children from the same areas were examined in 2003 and followed-up in 2010 to 2012.<sup>149</sup> At the follow-up, adolescents from both areas differed in their skin and nasal bacterial community compositions, being diversity higher in skin and nasal Russian samples. The abundance of *Acinetobacter* was on average 3 and 4 times higher on skin and nasal epithelium in Russian Karelia, as compared to Finnish adolescents.<sup>149</sup> The contrasts between US Amish and Hutterite population<sup>150</sup> as well as urban and rural Mongolia<sup>151</sup> have provided similar results. Despite the similar genetic ancestries, Amish and Hutterite children revealed marked differences in the prevalence of asthma. Compared with the Hutterites, the Amish, who practice traditional farming and are exposed to an environment rich in microbes, showed a 4 times lower rate of asthma and distinct immune profiles. In addition, the analysis of samples of mattress dust from Amish or Hutterite home showed different profiles in the abundance of bacteria.<sup>150</sup> In Mongolia, the prevalence of asthma, allergic rhinoconjunctivitis, and allergic sensitization was also low in rural areas and increased with increasing urbanization, suggesting that rural living environment confers protection against allergic diseases.<sup>151</sup>

The individual microbial composition and health tend to be affected by different environments. Supporting evidence is provided by studies showing that asthma and allergy are associated with lower environmental biodiversity and diversity in human microbiome composition. Hanski et al<sup>146</sup> reported that environmental diversity around adolescents' homes influenced the composition of bacteria in their skin and atopy. Forest, agricultural land, and species richness of native flowering plants were positively correlated with diversity of gammaproteobacteria and *Actinobacteria* on the skin of adolescents and negatively associated with atopy. In addition, a positive correlation was found between the relative abundance of gammaproteobacteria in skin healthy individuals and IL-10, one of the key anti-inflammatory cytokines in immunologic tolerance; however, a reverse correlation was observed in atopic individuals. Authors suggested that environmental biodiversity, human microbiome, and human immune system are complex systems that interact

with each other and that observed associations reflect immunologic responses developed by individuals with long-term exposure to environmental microbiome. Other studies highlighted the environment in which children grow up as an important factor affecting the composition of skin microbiome, which was related to their atopic diagnosis,<sup>153</sup> and suggest that the size of this effect varies with age.<sup>154</sup> In 2018, a canine model was considered to assess the association between exposure to environment, skin microbiome, and allergic symptoms. This model was adopted because dogs share and are influenced by the living environment and lifestyle of their owners, and suffer increasingly from allergic diseases, providing an empirical evidence of such interaction. Compared to dogs living in rural environments with a large family and frequent animal contacts, dogs living in urban environments and exposed to urban lifestyles, characterized by living in apartments, in a single-person family without other pets, have a higher prevalence of allergies. The composition of skin microbiome also differed in healthy and allergic dogs, being more heterogeneous in healthy dog families and associated with increasing area of arable land and forest in surroundings of birth and current home. Furthermore, the skin microbiome of dogs differed between rural and urban environments, suggesting that microbiome can have an important role in the development of allergic diseases.<sup>155</sup>

#### **Walkability in urban environment**

In the past few decades, increasing evidence suggests that features of the built environment are also associated with health-related behaviors such as physical activity, social connection, and environment protection.<sup>156</sup> A key concept is *walkability*, which includes a combination of built environment factors such as street connectivity, residential density, net area retail, and land use mix, that are conducive to walking (ie, walking to destinations, including work, school, shopping).<sup>157</sup> A high walkable neighborhood is characterized by high residential density, street connectivity, and high land use mix diversity,<sup>158</sup> being an indicator of how user-friendly a neighborhood area is for walking and biking.<sup>157</sup>

Living in neighborhoods characterized by higher walkability was found to be associated with more walking and cycling for transport and leisure, and with moderate to vigorous physical activity<sup>159</sup> and reduced obesity and overweight.<sup>160</sup> In children, high walkability is also positively associated with active park use and overall higher levels of physical activity. In a research on 13- to 15-year-old Belgian adolescents the average physical activity per day was associated with neighborhood walkability; adolescents living in high-walkable neighborhoods performed more moderate to vigorous physical activity than those who live in low-walkable neighborhoods, but only in low-socioeconomic status neighborhoods.<sup>161</sup> In 2011, Giles-Corti et al<sup>162</sup> developed a school walkability index considering the traffic exposure and reported that children attending schools located in highly walkable areas were 3.63 times (95% CI 2.01; 6.56) more likely to walk to school than those attending schools in low walkability areas. However, children living in areas with high street connectivity and traffic were significantly less likely to walk to school (OR=0.32, 95% CI 0.22; 0.47). Previous studies also showed a positive association between active school travel and healthier body composition and level of cardiorespiratory fitness in children.<sup>163</sup> Recently, Simons et al<sup>164</sup> reported an inverse association between home neighborhood walkability and incidence of asthma and ongoing asthma in Toronto children after adjustment for neighborhood and individual characteristics,

highlighting the level of physical activity as a possible mechanism of association between the lower neighborhood walkability and asthma. Furthermore, higher walkability around schools has been associated with positive attitudes toward children's neighborhood community, which were related to social interactions, social network, and sense of community.<sup>165</sup> Although features of neighborhoods, such as density, accessibility, and connectivity, may be predictors of air pollution levels,<sup>166</sup> walkable neighborhoods may also allow people to reduce their daily travel distance, by encouraging active and public transport modes, thereby decreasing vehicle emissions of air pollutants.<sup>167</sup>

### **Air pollution in urban environment**

Ambient air pollution and its health effects are also closely related with the scale of urbanization and the type and intensity of human activities. Cities at different stages of urbanization may have different sources of air pollution, including industry, transport, power generation, construction and household emissions.<sup>122</sup> For example, Denmark presents a satisfying urbanization growth with low air pollution (urbanization: 83.1%; air pollution intensity: 1.01 kt of CO<sub>2</sub> equivalent per hundred billion dollars). However, other countries, like Russia, presents high level of urbanization and a serious problem regarding air pollution (urbanization: 68.9%; air pollution intensity: 5.91 kt of CO<sub>2</sub> equivalent per hundred billion dollars), whereas Vietnam, maintain a low-level urbanization, air pollution has been a severe problem (urbanization: 21.7%; air pollution intensity: 5.66 kt of CO<sub>2</sub> equivalent per hundred billion dollars).<sup>168</sup> Concern about environmental health and effect of air pollution has been increasing since the great smog of London, which killed 4000 people over the course of a few weeks in 1952 and caused 12,000 excess deaths in the year after the event. The great smog of London half a century ago highlighted that air pollution can not only cause acute health effects but can also result in long-term effects.<sup>169</sup>

According to WHO, 9 out of 10 people now breathe polluted air, which kills 7 million people every year. An estimated 4.2 million premature deaths are linked to air pollution, mainly from heart disease, stroke, chronic obstructive pulmonary disease, lung cancer, and acute respiratory infections in children.<sup>170</sup> Children are at high risk of air pollution-related disease and even extremely low dose of pollutants during infancy and/or in early infancy can result in disease, disability, or death later in life.<sup>170</sup> Growing evidence supports the link between ambient air pollution exposure and the incidence of asthma in children. In a study involving 10 European cities, exposure to roads with high vehicle traffic were associated with 14% of all asthma cases in children and 15% of all exacerbations were attributed to exposure to road traffic pollutants.<sup>171</sup> In 2014, Guarnieri and Balmes<sup>172</sup> review the effect of different ambient air pollutants, including O<sub>3</sub>, NO<sub>2</sub>, SO<sub>2</sub>, and PM on development and exacerbation of asthma in children. Authors suggested that these pollutants might have irritant and inflammatory effects on airway neuroreceptors and epithelium. In addition, exposure to O<sub>3</sub> and NO has been reported as having an airway hyperresponsiveness effect.<sup>172</sup> In 2017, a meta-analysis, showed a positive association between asthma exacerbations and several air pollutants among children aged 0 to 18 years. In this subgroup, the association was significant for NO<sub>2</sub> (OR: 1.040; 95% CI 1.001; 1.081), SO<sub>2</sub> (OR: 1.047; 95% CI 1.009; 1.086), and PM<sub>2.5</sub> (OR: 1.022; 95% CI 1.000; 1.045).<sup>173</sup> A recent population-based study also found that early-life exposures to NO<sub>2</sub> (OR: 1.25; 95% CI 1.10; 1.41)

and PM<sub>2.5</sub> (OR: 1.25; 95% CI 1.06; 1.46) were positively associated with the risk of asthma development in childhood, per interquartile range (IQR) increase in each pollutant (NO<sub>2</sub> IQR = 8.51 ppb and PM<sub>2.5</sub> IQR = 4.43 μm<sup>3</sup>).<sup>174</sup> Alotaibi et al<sup>175</sup> estimated the number of new cases of asthma among children attributable to traffic-related air pollution in USA in 2000 and 2010. In 2010, the incidence of asthma due to traffic-related air pollution accounted for 18% (due to NO<sub>2</sub>) to 36% (due to PM<sub>10</sub>) of all cases. Most attributable cases clustered in urban areas, being particularly prominent for NO<sub>2</sub>. Moreover, authors found that children living in urban areas had twice the percentage of asthma cases attributable to NO<sub>2</sub> exposure as compared to children living in rural areas (30% vs 15% in 2000, and 20% vs 10% in 2010). Although the mechanisms by which pollutants induce the development or exacerbation of asthma are not completely clear, the UK's Committee on the Medical Effects of Air Pollutants proposed the following 4 mechanisms: (a) oxidative stress and airway damage; (b) airway remodeling; (c) inflammatory pathways and immunological responses; together with (d) enhancement of respiratory sensitization to aeroallergens.<sup>176</sup>

Urban greenspaces not only provide balance for ecosystems but can also act as a buffer against exposure to air pollution, by removing pollutants from the atmosphere.<sup>177,178</sup> In Strasbourg from July 2012 to June 2013, public trees removed about 88 tons of air pollution, which varies with pollutants, amount of tree cover, condition and size, and seasons.<sup>179</sup> In addition, sustaining healthy trees could improve air quality in cities by improving leaf surface area to remove pollutants by dispersing local pollutants or limiting dispersion toward sidewalks where people are often exposed to emissions of pollutants.<sup>179</sup> Similar results were observed in Gothenburg, Sweden,<sup>180</sup> and in 10 Italian metropolitan cities, authors found that concentrations of NO<sub>2</sub> and PAHs<sup>180</sup> and O<sub>3</sub> and PM<sub>10</sub>,<sup>181</sup> respectively, were affected by green areas. In contrast, Yli-Pelkonen et al<sup>182</sup> suggested that forest vegetation in near-road urban environments in Helsinki does not improve local air quality. Authors reported that concentrations of gaseous air pollutants, including NO<sub>2</sub>, O<sub>3</sub>, and anthropogenic VOC, did not differ between tree-covered and adjacent open areas, whereas PM levels were significantly lower in tree-covered areas than in adjacent open.

### **Conclusion**

There is growing recognition of the importance of the urban environment in pediatric asthma. Specifically, increasing evidence suggests that air pollution, indoors and outdoors, is associated with the increasing prevalence of asthma. This review underlines the role of urban environment on the development of asthma, demonstrating that behinds genetics, the dynamic interaction between the human being and health is determined by environmental interactions. Exploring the effects of indoor and neighborhood environments is crucial for planning, defining guidelines, and making recommendations to cities planners and decision makers to create healthier and sustainable urban environments, with potential to protect citizens against the development of asthma and allergic diseases. In addition, future research should focus on assessing the cumulative effect of several exposures, namely different indoor and outdoor environments, over time.

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## Conflicts of interest

The authors declare no conflicts of interest.

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