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The role of environmental factors in childhood asthma

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Background: Asthma is a common chronic respiratory disease affecting people worldwide. The prevalence, incidence, mortality and economic burden of asthma have increased since 1960 in developed countries, especially among children. Although higher asthma-related mortality rates occur in low- and middle-income countries. Childhood-onset asthma is typically allergic and accompanied by other allergic diseases such as atopic dermatitis, allergic rhinitis or food allergy. It is well acknowledged that genetic and environmental factors contribute to development of asthma. Research has been conducted about different environmental factors and their protective as well as predisposing effects. These studies focus mainly on prenatal period along with early years of life. Understanding the effects of environmental factors could possibly help us prevent several childhood-onset asthma cases.

Aim: to review current data on the effect of environmental factors on childhood asthma.

Methods: A database search on PubMed was carried out to summarize the effects of antibiotic usage, exposure to outdoor air pollution as well as farming environment and greenery on the incidence of childhood asthma. Studies published in English between 2017-2023 were selected. In addition, one older study from 2006 was included. All studies focused on children or included a child population (ages 0 to 18 years)

Results: Altogether 16 original studies and two meta-analyses were included. Meta-analyses were used to support the results. Exposure to antibiotics during pregnancy and early years of life was associated with increased risk of childhood asthma. Exposure to outdoor air pollution during early life resulted in higher risk of developing childhood asthma. Living in rural area and being exposed to farming environment was associated with lower risk of asthma, although when viewing specifically effects of greenery, the results remained inconsistent.

Conclusions: Based on these studies, minimizing the use of unnecessary antibiotics during early life may have protective effect on childhood asthma. In addition, by focusing on sustainability especially when it comes to traffic, the incidence of asthma could be decreased. Being exposed to farming environment seems to play a protective role, although a single study reported that farming environment didn't seem to have protective effect on the long run, as the exposure increased the odds of later diagnosed asthma. When it comes to exposure to greenery, results remained conflicting and thus need further research.

Key words: asthma, antibiotics, outdoor air pollution, rural, farming, greenery

Table of contents

1 Introduction

Asthma is a common chronic respiratory disease affecting up to 18% of people worldwide. Bronchoconstriction, airway wall thickening and increased mucus production together cause variable expiratory airflow. Typical symptoms include wheezing, cough and shortness of breath. These symptoms are often triggered by different irritable factors including exercise, allergen exposure, respiratory infections and change in temperature and humidity. (GINA: Main Report 2022.)

The prevalence, incidence, mortality and economic burden of asthma have increased in developed countries since 1960, especially among children. Nevertheless, higher asthma-related mortality rates occur in low- and middle-income countries. (Dharmage et al. 2019.) Increasing number of hospital admissions caused by asthma may be due to increase in disease severity, poor asthma management or the cause of poverty (Serebrisky et al. 2019).

Many factors, such as genetics and environment, contribute to development of asthma and other allergic diseases, such as eczema and allergic rhinitis. Allergic asthma typically starts in childhood and is usually persistent even though disease severity tends to vary in time. (Akar-Ghibril et al. 2020.) In addition, changing environmental agents seem to play a substantial part in rising asthma prevalence (Dharmage et al. 2019). This has been a topic that has gained even more attention among researchers. Urbanization and industrialization have contributed to increased outdoor air pollution. Studies have shown that children living in urban areas have increased risk of asthma symptoms and exacerbations, asthma hospitalizations and new-onset asthma compared to those living in rural areas. Research has also shown that indoor dampness and mold growth are associated with larger asthma incidence and prevalence. (Serebrisky et al. 2019.) Still, there seems to be stronger evidence on the role of environmental agents as asthma triggers rather than causes (Dharmage et al. 2019). It is also known that antibiotics alter both gut and lung microbiota further causing dysbiosis as well as reduced microbial diversity. This seems to be significant cause of increasing asthma prevalence. (Hufnagl et al. 2020.)

Hygiene hypothesis today has extended to also include biodiversity hypothesis. Biodiversity hypothesis suggests that exposure and contact with nature and environment improves the diversity of human microbiota, promotes immunological homeostasis and protects from allergic diseases. (Haahtela 2019.) However, data is scarce on how exposure to greenery during early years of life affects the development of asthma. In addition, there seems not to be research on how exposure to greenery during pregnancy affects the child and its tendency to atopic diseases. Furthermore, current research doesn't have clear evidence that a specific type of antibiotic would have greater effect on the incidence of asthma.

This review summarizes the effects of different environmental factors on the development of childhood asthma. The environmental factors discussed are exposure to antibiotics, outdoor air pollution and biodiversity (farming environment, dampness, mold and greenery). Our hypothesis is that these environmental factors have either protective or risk increasing effect. Most importantly, this review elaborates on whether we can somehow prevent or minimize the risks of childhood asthma.

2 Methods

As a part of this review we performed some practical work at Turku University Hospital (TYKS) as a part of Fish Oil and Probiotics in Pregnancy (FOPP) study from 2020 to 2022. The practical work included execution of spirometry with bronchial dilation test to children aged 5-6 years old. The spirometry test results will be used in further studies.

A database search on PubMed was carried out to summarize the effects of antibiotic usage, exposure to outdoor air pollution, farming environment and greenery on the onset of childhood asthma. Apart from one study, only studies published in English between 2017-2023 were selected. For articles about antibiotics following search terms were applied: ("antibiotic*" OR "anti-bacterial agents"[Mesh]) AND ("prevent*" OR "risk*") AND ("child*" OR "Child"[Mesh]) AND ("asthma" OR "Asthma"[Mesh]). For outdoor air pollutants search terms were: ("outdoor" OR "air pollutant*" OR "gas*" OR "chemical*" OR "particulate matter" OR "black carbon" OR "nitrogen dioxide" OR "ozone" OR "carbon monoxide" OR "sulfur dioxide" OR "microplastic" OR "plastic*" OR "polyethylene" OR "polyvinyl" OR "polypropylene" OR "Air Pollutants"[Mesh]) AND ("prevent*" OR "risk*") AND ("child*" OR "Child"[Mesh]) AND ("asthma" OR "Asthma"[Mesh]) . For rural living and exposure to greenery search terms were: ("rural" OR "countryside" OR "green*" OR "vegetation" OR "plants" OR "mold" OR "pets" OR "animal*") AND ("prevent*" OR "risk*") AND ("child*" OR "Child"[Mesh]) AND ("asthma" OR "Asthma"[Mesh]).

In addition, a few articles outside the search were included to complement the etiology of asthma and pathophysiology behind the environmental factors. For outdoor air pollutants one larger study outside the search terms was selected. An older study from 2006 was included in order to demonstrate the effects of living near a major road. All studies focused on children or included child population (ages 0 to 18 years).

3 Review of the literature

3.1. Antibiotics

Our gut is home to several microorganisms including bacteria, archaea, viruses and fungi (von Mutius et al. 2020). These commensals are essential for immune homeostasis by producing protective mucus and antimicrobial agents (Belkaid et al. 2017). In addition, the intestine plays a major role in immune cell development (McAleer et al. 2018). Antibiotics are well known to alter gut microbiota by reducing its natural diversity. Intestinal dysbiosis enhances lung inflammation caused by allergens and infections. (Loewen at al. 2018.) Impairment of the natural intestinal microbiota, especially when occurring early in life, is related to onset of childhood asthma. Therefore, not only is intestinal dysbiosis affecting gastrointestinal tract, but also lungs. This can be explained by the gut-lung axis, meaning the bi-directional communication between these two organs. (Hufnagl et al. 2020.)

Main characteristics of studies investigating the health effects of antibiotics are summarized in Table 1. A recent meta-analysis included 52 studies that investigated the association between early age antibiotic exposure and childhood asthma. The total analysis showed that antibiotic exposure before the age of three and onset of childhood asthma are indeed related: odds ratio (OR) being 1.4; 95% confidence interval (CI) 1.3–1.5. Antibiotic exposure during the first week of life had the strongest outcome (OR, 1.8; 95% CI, 1.3–2.5). The study also looked into different antibiotic types. Macrolides led to stronger risk of asthma-outcome (OR, 1.56; 95% CI, 1.3–1.9) than cephalosporin (OR, 1.4; 95% CI, 1.2–1.6) and penicillin (OR, 1.3; 95% CI, 1.2–1.5). Not only the type of antibiotic, but also the amount of prescriptions affected the risk of childhood asthma. An increased risk was discovered when prescriptions increased from 1 to 2 (OR, 1.3; 95% CI, 1.2–1.4) to 3-4 (OR, 1.8; 95% CI, 1.5–2.1) and tableland after 5+ prescriptions (OR, 1.8; 95% CI, 1.4–2.4). (Zhang et al. 2021.)

In a Chinese cross-sectional study exposure to antibiotics during first year was associated with increased odds of asthma (OR 1.6, 95% CI 1.4–1.8) (Zou et al. 2020). Another large study discovered that among children who were prescribed one to two antibiotic treatments during the first two years of life, only girls were at significantly higher risk to develop asthma compared to the unexposed control group. However, being given three or more prescriptions was associated with a higher incidence of asthma in both sexes. When it came to antibiotic type, use of penicillin had the strongest connection to childhood onset-asthma ($p<0.001$ in females and $p=0.001$ in males). (Aversa et al. 2021.) Likewise, in a Finnish study infants (age 0-11 months) receiving two or more antibiotic prescriptions had a 4.0% increase in the total risk of developing asthma by the age of seven ($p=0.006$) (Toivonen et al. 2021).

A population-based retrospective cohort study in Canada studied the effects of maternal antibiotic usage during pregnancy. Children exposed to prenatal antibiotics had significantly higher rates of asthma compared to the unexposed group. In this study, prenatal antibiotic exposure had a dose-dependent risk on childhood asthma (aHR, 1.2; 95% CI 1.1–1.2) for 1 exposure, (aHR, 1.3; 95% CI 1.2–1.3) for 2 exposures and (aHR, 1.5; 95% CI 1.4–1.6) for 3 or more exposures. (Loewen et al. 2018.) In another large population-based cohort study antibiotic use during pregnancy was associated with childhood asthma (HR 1.2, 95% CI 1.2–1.2) (Momen et al. 2021.)

Summary: Early life antibiotic exposure increases the risk of new-onset childhood asthma. Intestinal dysbiosis and impairment of gut flora leads to increased risk of childhood asthma by immunological mechanisms, although the exact mechanisms of gut-lung axis are still not fully comprehended and need more research. The risk of childhood asthma seemed to be associated with dose-dependent use of antibiotics, whereas it wasn't clear which type of antibiotic caused the highest risk. Based on these studies, we should minimize the use of unnecessary antibiotic treatments during pregnancy and early childhood.

3.2. Outdoor air pollution

Growing evidence indicates that air pollution plays a significant role in asthma development. The biological mechanisms can be explained by oxidative stress and cytokine production. Reactive oxygen species (ROS) result in inflammation, airway hyperactivity and tissue injury. Whereas cytokines promote IgE production and T-cell differentiation. Outdoor air pollution consists of numerous pollutants, such as nitrogen dioxide (NO2), carbon monoxide (CO), sulfur dioxide (SO2) and particulate matter (PM). NO2 and SO2 are primarily traffic-related and released from burning fossil fuel. CO is caused by incomplete burning of natural gas and other carbon-containing products. PM is a mixture of solids and liquids such as smoke, dirt and soot from natural and manufactured sources. PM can be divided to categories based on its diameter: PM 0.1 (<0.1 um), PM 2.5 (0.1-2.5 um) and PM10 (2.5-10 um). In this chapter we are mainly focusing on the asthma-inducing effects of PM2.5 and NO2. (Khreis et al. 2019.)

Studies examining the health effects of outdoor air pollution are summarized in Table 2. A large study covering 18 European countries estimated that PM2.5 exposures could be held responsible for as much as 33% of asthma cases in 18 European countries with children aged 1-14 years. Some of these could possibly be prevented by agreeing with World Health Organization's (WHO) air quality guideline values for NO2 and PM2.5. WHO publishes a numerical value to indicate a concentration of a certain air pollutant and connects it to a time of exposure. When concentration stays below this concerned level, health effects should be minimal or non-existent. For children aged 1-4 years, complying to WHO's NO2 guidelines was approximated to prevent 0.4% of annual cases of childhood asthma. **(**WHO global air quality guidelines 2021.) (Khreis et al. 2019.)

Many other studies advocate the connection between PM2.5 exposure and onset of childhood asthma. An American study found that a natural log increase in mobile source PM2.5 during first year of life increased asthma risk by an absolute 1.2% by the age of 2. Whereas by the age of 5 the risk had increased by an absolute 4.1%. Corresponding effect estimates were made for NOx and CO. (Pennington et al. 2018.) In a Canadian study exposure to outdoor PM2.5 during pregnancy and early years of life was associated with increased incidence of childhood asthma (Hazard Ratio for each 1 μg/m3 increase = 1.026, 95% CI: 1.021–1.031). (Lavigne et al. 2021). In a smaller study the interquartile range (IQR) increase in NO2 exposure during prenatal and early postnatal period increased the likelihood of later childhood asthma by 25%. Correspondingly, IQR increase in early PM2.5 exposure resulted in 1.25 times greater odds in receiving the diagnosis. **(**Kravitz-Wirtz et al. 2018.**)** In a Swedish population, exposure to PM2.5 and two other components, primary organic carbon (pOC) and secondary organic aerosols (SOA), during the first three years of life resulted in increased asthma occurrence in the first six years of life. Whereas exposure during foetal life or the first year of life did not significantly increase the asthma risk, as HR was close to one. (Olsson et al. 2021.)

In an older study McConnel et al. (2006) examined the relationship between traffic and asthma in Californian school children. Living within 75 meters of a large road led to increased risk of lifetime asthma (OR 1.3; 95% CI, 1.0–1.9), prevalent asthma (OR = 1.5; 95% CI, 1.2–2.0), and current wheeze (OR = 1.4; 95% CI, 1.1–1.8). Whereas children who lived within 150-300 meters of the major road had lower odds for lifetime asthma (OR =0.9; 95%CI, 0.7–1.2). When it came to prevalent asthma and current wheeze, odds ratio remained close to one. Studies have shown that largest concentrations of traffic-related pollutants appear within 150-200 meters from the large road and decline from there on.

Summary: Studies show that exposure to air pollution during pregnancy and early life increases the risk of asthma onset in children. Traffic is a major source of PM2.5 and NO2, thus living in large crowded cities with diverse road networks is a risk factor for developing asthma at a young age. If we want to minimize the risks, we should pay more attention to our actions concerning transportation, waste management, recycling and energy usage, which all are major sources of air pollutants. In addition, living at least 300 meters from a major road may protect from childhood asthma as concentrations of air pollutants are higher near roadways.

3.3. Biodiversity (farming environment, dampness, mold and greenery)

As known, the environment in rural areas differs quite a bit from urban cities. For example, houses tend to be older, which may cause mold growth. Furthermore, wood-burning is more common. Both of these are known as asthma triggers. On the other hand, outside air quality in rural areas is better compared to urban cities and exposure to air pollutants is minor. Moreover, vegetation in rural areas is more diverse. It is suggested that surrounding vegetation might have a protective role as it improves air quality by mitigating air pollution. Air pollution might be absorbed by the leaves of trees. (Yu et al 2021.) Studies have also shown that living in a small farm works as an asthma-protective factor. Exposure to dust, animal sheds and other microbial agents increase the diversity of nasal microbiota. (Estrada et al. 2017.) Furthermore, the upper airways mirror the microbiota of the lower airways, the inflammatory location in asthma (Depner et al. 2017). Broad spectrum of microbes in environment, lungs and skin is known to support healthy immune homeostasis and lead to lower prevalence of allergic diseases (Frei et al. 2022). We looked into the effect of farming environment, mold and greenery on childhood asthma. The summary is presented in Table 3.

Farm environment: It remains unclear, whether rural living plays a protecting a role in the onset of asthma. A meta-analysis covering 27 studies found that living among farm animals and being exposed to fodder during pregnancy and early life might have a protective effect on asthma although the exact protecting mechanism still remains unclear. (Pechlivanis et al. 2021.) A Finnish study investigated whether childhood exposure to farming environment would affect the outcome of asthma. Those exposed to farming environment had lower odds for early asthma diagnosis (aOR, 0.5; 95% CI, 0.3–0.8) compared to children living in non-farming environments. However, farming environment did not seem to have a protective effect on the long run, as the exposure increased the odds of later diagnosed (40-60 years) asthma (aOR, 2.3; 95% CI, 1.1–4.7). (Andersén et al. 2021.) A Canadian study found similarly, that compared to large urban region, people living in small urban region (OR 0.7, 95%CI: 0.5-1.1) and rural region (OR 0.6, 95% CI: 0.4-0.8) had less children with ever-diagnosed asthma, p-value for trend being <0.001 (Lawson et al. 2017).

Dampness and mold: Exposure to dampness and mold is associated with increased odds of asthma. These factors are commonly linked to dust mites, bacteria and organic chemicals due to rotting of building materials. Houses in rural area tend to be older and have more often poor heating systems, which may cause dampness and mold growth. (Wang et al. 2019.) A study investigated how perinatal factors affected childhood allergic diseases, such as asthma. Exposure to visible mold or damp stain in child's perinatal period was associated with greater odds of childhood asthma. Conversely, contact with cats or dogs was not a statistically significant factor. (Ellie et al. 2021.)

Greenery: A cross-sectional Chinese study of 59,754 school children investigated, whether vegetation plays a protective role in asthma development among school children. The study took children's schools as study sites and made 800 m and 1000 m circular buffers to indicate exposure to greenness. Greenspace was indicated by GVI (green view index): higher number indicating a larger green coverage on the area. The study showed, that an IQR increase in GVI800 m (trees) was associated with 24% (95%CI: 20–28%) lower odds for diagnosed asthma and 18% (95%CI: 11–25%) lower odds for current asthma. On the other hand, IQR increase in GVI800m (grass) was associated with 4% (95%CI: 0–8%) higher odds for diagnosed asthma and 8% (95%CI: 2%–14%) higher odds for present asthma. (Yu et al. 2021.) On the contrary, a smaller case-control study discovered that increased level of greenness was associated with higher risk of asthma occurrence in preschool children (Hsieh et al. 2019).

When it comes to nasal microbiota, numerous studies have speculated that early colonization of Haemophilus influenzae, Moraxella catarrhalis, and Streptococcus pneumoniae of upper respiratory tracts contributes to the development of childhood wheeze. Depner et al. (2017) studied the effects of farming on nasal microbiota and asthma outcome. They found that compared to healthy controls, asthma was associated with diminished α- and β-diversity of the nasal microbiota and the abundance of Moraxella (alpha diversity meaning species diversity in a specific area and beta-diversity meaning the difference in diversity between two or multiple ecosystems). However, in farm children Moraxella colonization did not affect the asthma outcome.

Summary: Living in rural area seems to have a protective effect on childhood asthma. Exposure to farming environment and living in rural area predispose us to a wide spectrum of microbes. This further leads to protective effect of healthy immune homeostasis and increased diversity of nasal microbiota. As regards to greenness and vegetation, studies remain inconsistent whether there is an association with childhood asthma prevalence. A single study discovered that association between trees and grass had opposite effect on asthma onset. Trees acted as a protective factor whereas grass seemed to be predisposing factor. One reason for these results might be the fact that grass pollen can act as an allergen and cause asthma. At any rate, planting trees in cities and near road networks could reduce asthma prevalence when pollution is under control.

4 Discussion

This literature review assessed the evidence on correlation between environmental factors and childhood asthma. Main findings of this literature review are 1) Exposure to antibiotics during pregnancy and early years of life increase the risk of developing childhood asthma. 2) Exposure to outdoor air pollution (PM2.5 and NO2) during early years of life increases the risk of developing childhood asthma. Exposure to such pollutants during pregnancy may increase the risk of asthma. 3) Living in rural or greener area may have a protective effect against childhood asthma. A single study showed that trees acted as a protective factor whereas grass seemed to be a predisposing factor. The effects of vegetation on childhood asthma will need further investigation.

This review covered five original researches that investigated the association between antibiotic exposure and childhood asthma. Antibiotics are known to alter gut microbiota and lead to increased risk of childhood asthma. In a healthy gut, microbial antigens are represented to human immune system by dendritic cells. Dendritic cells (DC) promote the development of regulatory T cells and natural killer cells (NK). NKs normally suppress T-helper cell 2 (Th2) inflammation and regulatory T cells account for suppressing immune responses. Antibiotics kill healthy microbiota and lead to lower bacterial diversity and an inflammatory site without DCs or NK cells. This kind of environment will promote the elevation of immunoglobulin-E levels, increase the amount of basophils and aggravate basophil induced Th2 responses. (Ferreira et al. 2014.) In the light of newest research, dysbiosis caused by antibiotics may last 2 years after the exposure (Kesavelu et al. 2023).

In all studies included, exposure to antibiotics during the first years of life was associated with increased risk of childhood asthma (Table 1.) A recent meta-analysis by Zhang et. al (2021) supports this claim, as children exposed to antibiotics before the age of three had higher odds of developing asthma (OR 1.4; 95% CI 1.3–1.5). The risk of asthma seems to rise as the amount of antibiotic courses increases. Even when antibiotic courses increase from 1 to 2, the odds of developing asthma rise significantly (OR, 1.3; 95% CI, 1.2–1.4). Of these five studies two focused on maternal use of antibiotics (Loewen et al. 2018, Momen et al. 2021). Exposure to antibiotics in utero similarly increased the risk of childhood asthma onset.

All the study results are in line with each other and support the claim that early life antibiotic exposure is associated with increased risk of childhood asthma around the world. The data is still scarce on whether a specific antibiotic type has a greater predisposing effect. Although in a recent systematic review and meta-analysis discovered that exposure to more broad-spectrum antibiotics, macrolides, was associated with reduced intestinal biodiversity for twice as long compared to penicillin. (McDonnell et al. 2021.)

This review also covered six researches studying the relation between outdoor air pollution and childhood asthma. The air pollutants we mainly focused on were PM2.5 and NO2. Studies show that air pollution will not only trigger asthma symptoms but might also be the cause of new-onset asthma. The respiratory mucosa acts as a barrier against air pollutants. When encountering respiratory mucosa, pollutants tend to trigger immunological defence mechanisms, which lead to activation of oxidative stress and pro-inflammatory cytokine expression. ROS induce airway inflammation, hyperreactivity and injury. Whereas cytokines will promoter Th2 differentiation and inflammation as well as IgE production. (Tiotiu et al. 2020.)

Evidence shows that exposure to such pollutants during early years of life results in higher risk of developing childhood asthma (Table 2). Four out of six studies were conducted in North America and one study from Sweden was included. Although majority of research took place in North America, a study including 18 European countries discovered the same effect of air pollutants. An older study from 2006 showed that children living within 75 meters from a major road had higher risk of ever diagnosed asthma, prevalent asthma and current wheeze compared to those living further away from the road (McConnel et al. 2006). Two of the studies reported that exposure to PM2.5 and NO2 during pregnancy increases the likelihood of childhood asthma (Lavigne et al. 2021, Pennington et al. 2018) whereas one of the studies didn’t find exposure during fetal life significant (Olsson et al. 2021). At any rate, we should be paying more attention to our actions concerning transportation, waste management, recycling and energy usage, which all are major sources of air pollutants. In addition to slowing down climate change, these actions will minimize the risk of asthma onset.

Living in rural area differs quite a bit from urban living. Air quality in rural area tends to be cleaner and vegetation is more diverse. In farming environment children are possibly exposed to animal sheds and dust. Houses tend to be older and are more often affected by dampness and mold growth. According to biodiversity hypothesis, abundant microbial diversity is associated with better immune homeostasis and tolerance (Haahtela 2021).

This review included 5 original studies that investigated the effects of farming environment, dampness and greenness on childhood asthma. Studies investigating exposure to rural and farming environment were conducted in Finland and Canada. Studies regarding greenery were carried out in East Asia. According to (Lawson et al. 2017.) people living in small urban region and rural region have less children with diagnosed asthma. A recent meta-analysis supports this claim that living among farm animals and being exposed to fodder during pregnancy and early life might have a protective effect on asthma (Pechlivanis et al. 2020). Exposure to dampness during child's perinatal period led to greater odds of childhood asthma (Ellie et al. 2021). When it comes to greenery, studies show inconsistent results and thus will need further investigation. Yu et al. (2021) discovered that larger green coverage (trees) on area was associated with lower odds for diagnosed asthma, whereas larger green coverage (grass) was associated with higher odds for diagnosed asthma. Hsieh et al. (2019) found that increased level of greenness was associated with higher risk of asthma occurrence in preschool children.

It seems that living in rural area has both protective and risk increasing effects depending on what component of rural living is contemplated on. Furthermore, it must be acknowledged that lower asthma prevalence in rural areas could be attributable to underdiagnosis. In a single study exposure to larger grass coverage led to greater odds for childhood asthma. One possible reason to explain this is the fact that grass pollen can act as an allergen and thereby cause asthma. Data also seems to be scarce on how exposure to greenery during pregnancy affects the child and its tendency to atopic diseases.

Westernized lifestyle has caused many health problems, such as higher rates of asthma and allergic diseases. Urbanization and industrialization have led to increased levels of air pollution. In this literature review we proved the connection between environmental factors and new-onset childhood asthma. Farming environment and exposure to larger green area (trees) acted as protective factors. Exposure to antibiotics, outdoor air pollution, mold and green area (grass) had a predisposing effect on asthma onset. These all are factors that should be taken into consideration for example when planning urban residencies. Prescribing antibiotics according to current guidelines could prevent many childhood asthma cases.

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Attachments

Table 1. Antibiotic exposure and the outcome of childhood asthma.

Reference	Country	N	Age	Intervention	Outcome	Design	Results	Conclusion
Loewen et al. 2018	Canada	213661	5-17 years	Exposure to antibiotics during pregnancy and dose	Asthma after the age of 5	Population-based cohort study	HR 1.29 (95% CI 1.26–1.33) aHR 1.15 (95% CI 1.11–1.18) for 1 exposure, aHR 1.26 (95% CI 1.21–1.33) for 2 and aHR 1.51 (95% CI 1.44–1.59) for 3 or more	Higher risk of childhood asthma Increased risk of asthma for each additional exposure.
Aversa et al. 2020	USA	14,572	0-14 years	Antibiotic exposure during first 2 years of life and dose	Asthma by the age of 14	Population-based cohort study	HR (95% CI) 1-2 prescriptions: females 1.57 (1.20–2.05), males 1.28 (1.01–1.61), 3-4 prescriptions: females 1.85 (1.37–2.50), males 1.92 (1.52–2.44), 5+ prescriptions: females 3.00 (2.31–3.90), males 2.24 (1.81–2.78)	Only girls were at significantly higher risk. Higher incidence of asthma in both sexes.
Toivonen et al. 2020	Finland	697	0-7 years	Exposure to antibiotics during first 0-11 months and dose dependency	Asthma by age 7	Population-based birth-cohort study	Absolute risk increase: 4% (95% CI: 0.9-7.2%), p=.006	Exposure to ≥2 antibiotic treatments was associated with increased risk of asthma
Zou et al. 2020	China	13,335	4-6 years	Exposure to antibiotics during first year	Asthma at age 4-6	A cross-sectional study	OR 1.57, (95% CI: 1.39-1.78)	Higher risk of asthma

Momen et al. 2021	Denmark	407804	0-6 years	Exposure to antibiotics during pregnancy	Asthma after the age of 5	Population-based cohort study	HR 1.21, 95% CI 1.18–1.24	Higher risk of asthma
Zhang et al. 2021		2 742 140	1-18 years	Exposure to antibiotics during first 3 years of life Dose	Asthma at 1-3 years and at >6 years	Meta-analysis	OR 1.84 (95% CI 1.63-2.08) OR 1.11 (95% CI: 0.96-1.28) Antibiotic course increase from 1 to 2: (OR 1.29; 95% CI, 1.18–1.42) to 3-4 (OR, 1.79; 95% CI, 1.49–2.14) and to 5 (OR, 1.79; 95% CI, 1.36–2.36)	Risk of asthma was higher at younger age and became insignificant at >6 years old. There was a dose-dependent response until 3-4 courses.

Table 2. Outdoor air pollution and the outcome of childhood asthma.

Reference	Country	N	Age	Intervention	Outcome	Design	Results	Conclusion
McConnel et al. 2006	US	5,341	5-7 years	Living within 0-75 m of a major road Living within 150-300 m of a major road	Ever diagnosed childhood asthma, prevalent asthma or current wheeze	Cohort study	(OR = 1.29; 95% CI, 1.01–1.86) for ever diagnosed asthma, (OR = 1.50; 95% CI, 1.16–1.95) for prevalent asthma and (OR = 1.40; 95% CI, 1.09–1.78) for current wheeze (OR 0.92; 95%CI, 0.73–1.15), (OR 1.04; 95% CI,0.82-1.33) and (OR 1.02;95%CI 0.82-1.27)	Increased odds of ever diagnosed asthma, current asthma and wheeze. Lower odds of ever diagnosed asthma, current asthma and wheeze.
Kravitz-Wirtz et al. 2018	US	4535	0-18 years	Exposure to air pollution during prenatal and postnatal period	Asthma	Population-based, multigenerational panel dataset	NO2: OR 1.25, (95% CI: 1.10-1.4) PM2.5: OR 1.25 (95% CI: 1.06-1.46)	An IQR increase in NO_2 and $PM_{2.5}$ exposure increased the odds of childhood asthma
Pennington et al. 2018	US	24,608	0-6 years	Exposure to primary mobile source pollutants during pregnancy and first year of life	Asthma at age 2-6 years	Birth cohort	Risk of asthma by age 2 increased by 1.2% (95% CI: 0.0%-2.3%) and by age 5 the risk increased by 4.1% (95% CI=1.6%, 6.6%)	When first year of life PM2.5 increased by a factor of 2.7 (a natural log increase), risk of asthma increased by the age of 2 and 5.

Khreis et al. 2019	18 European countries	63442419	1–14 years	Exposure to outdoor air pollution (NO_2, $PM_{2.5}$ and BC)	Asthma at age 1-14 years	Mathematical modelling	Reaching the minimum air pollution level for $PM_{2.5}$, BC and NO2 were estimated to prevent 33%, 15% and 23% of all annual cases of childhood asthma.	Air pollution is associated with childhood asthma
Lavigne et al. 2021	Canada	1,130,855	0-6 years	Exposure to PM2.5 during pregnancy and childhood	Asthma by age 6	Population-based cohort study	HR for each 1 µg/m3 increase = 1.026, 95% CI: 1.021–1.031)	Increased incidence of childhood asthma
Olsson et al. 2021	Sweden	163,740	0-6 years	Exposure to air pollution during pregnancy and first 3 years of life	Asthma at age 0-6 years	Cohort study	The HRs (95% CI) of asthma in association with an IQR increase in PM2.5, pOC and SOA: 1.06, (1.01–1.10), 1.05, (1.02–1.09) and 1.02, (1.00–1.04)	Exposure to PM2.5 and the components pOC and SOA during the first 3 years of life were associated with increased asthma incidence.

Table 3. Exposure to farming environment or greenery and the outcome of childhood asthma.

Reference	Country	N	Age	Intervention	Outcome	Design	Results	Conclusion
Lawson et al. 2017	Canada	3509	5-14 years	Living in rural vs urban region	Asthma at 5-14 years	Cross-sectional study	For small urban region (OR 0.74, 95%CI: 0.51-1.07) and rural region (OR 0.57, 95% CI: 0.44-0.75), p-value for trend <0.001	Children living in small urban region and rural region had less children with ever-diagnosed asthma.
Hsieh et al. 2019	Taiwan	5062	0-5 years	Exposure to greenness	Asthma at 0-5 years	Case-control study	p-value for trend 0.0828	The risk of asthma occurrence increased significantly in preschool children as the level of greenness exposure increased.
Ellie et al. 2021	China	7366	0-8 years	Perinatal exposure to visible mold or dampness	Asthma at 0-8 years	Cross-sectional study	aOR (95%CI) 1.70 (1.12–2.57)	Increased odds of childhood asthma
Yu et al. 2021	China	59,754	2-17 years	An IQR increase in GVI800m (trees) An IQR increase in GVI800m (grass)	Asthma at 2-17 years	Cross-sectional study	Trees: 24% (95%CI: 20–28%) lower odds Grass: 4% (95%CI: 0–8%) higher odds	Lower odds for diagnosed asthma. Higher odds for diagnosed asthma.
Andersén et al. 2021	Finland	3864	0-11 years	Exposure to farming environment	Early asthma diagnosis (0–11 years)	Cross-sectional population-based study	aOR, 0.49; 95% CI, 0.30–0.80	Lower odds for early diagnosis of asthma