Short- and long-term effects of ambient air pollution on asthma in European urban and rural areas

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1. ABSTRACT

Exposure to ambient air pollution causes effects on the development of many diseases including respiratory diseases. One such respiratory disease is asthma. Many studies already determined negative effects of air pollution exposure on asthma. Yet, most of these studies in Europe were done in urban areas. In this literature review, short- and long-term effects of ambient air pollution on asthma development and exacerbation in European rural and urban areas were studied. Based on a preliminary study, it was decided to focus on single-pollutant effects of five air pollutants: $PM_{2.5}$, PM_{10}, NO_2, O_3 and SO_2. It was hypothesized that exposure of NO_2 and PM would mainly have negative effects in urban areas, O_3 mainly in rural areas and SO_2 in both type of areas. Sixteen studies were selected using a clear search strategy. Only one of these studies addressed differences between rural and urban areas in their results. Results of this study suggested that the expected effects of NO_2, PM and O_3 exposure could only be confirmed on the long-term. The other fifteen studies indicated mainly negative effects of NO_2 and PM exposure, both on the short- and long-term. Differences between effects of $PM_{2.5}$ and PM_{10} were debatable. Effects of SO_2 were studied too little to give a conclusive answer. For future research, it is recommended to consider rural areas more and examine multi-pollutant models that include demographics such as age.

KEY WORDS: AIR POLLUTION, AIR POLLUTANTS, ASTHMA, PARTICULATE MATTER, NITROGEN DIOXIDE, OZONE, SULFUR DIOXIDE, URBAN, RURAL, SHORT-TERM, LONG-TERM

2. LAYMEN SUMMARY

Air pollution has a huge impact on public health. It has been estimated that 8.8 million people die each year due to air pollution exposure. The main reason for this, is because exposure causes development of many diseases, including respiratory diseases. One very common respiratory disease which also has been linked to air pollution is asthma. Asthma is a persistent inflammation of the airways that along with narrowing of the airways can cause shortness of breath. In severe cases, this may lead to hospitalization, cancer or death. There are already quite some studies that examined the effects of certain air pollutants on the development of asthma. However, many of these studies in Europe were done in urban areas. Nevertheless, this does not mean that there are no effects in rural areas. Air pollutants concentrations, also in rural areas, often exceed World Health Organization (WHO) advices. Therefore, the aim of this literature review was to examine the short- and long-term effects of ambient air pollution on asthma development and exacerbation in European rural and urban areas. Based on a preliminary study into the types and sources of air pollution, it was decided to focus on effects of five air pollutants: nitrogen dioxide (NO_2), ozone (O_3), sulfur dioxide (SO_2) and two different types of particulate matter (PM). Particulate matter is a mixture of solid and liquid particles found in the air that can vary in composition and size. It was hypothesized that PM and NO_2 exposure would mainly cause negative effects in urban areas as they have traffic as their main source. In contrast, negative effects of O_3 were expected to dominate in rural areas as concentrations there are often higher. Effects of SO_2 were expected to be negative in both urban and rural areas as their main source, factories, can be present in both areas. To investigate this, a clear search strategy was conducted. Based on this strategy, sixteen studies were selected. Of these studies, only one investigated the effects of air pollution exposure in urban and rural areas. The effects shown by this study confirmed the hypothesis for PM, NO_2 and O_3, but only on the long-term. The other fifteen studies, that were conducted in mainly urban areas, showed that PM and NO_2 exposure is associated with negative effects, both on the short- and long-term. Furthermore, they showed that effects in terms of risk size were similar for PM and NO_2. Effects of O_3 and SO_2, on the other hand, were not clear. Overall, it was concluded that there are too little studies done on air pollution exposure in European rural areas. Furthermore, PM and NO_2 showed to have the clearest negative effects on asthma. Nevertheless, there should be future research into this topic. Not only to examine the effects of air pollution in rural areas more, but also to examine the interactions between air pollutions and the effects of demographics, like age and gender.

3. INTRODUCTION

Air pollution is a major threat for public health. Exposure contributes to respiratory diseases and to several non-communicable diseases such as cardiovascular diseases and diabetes type 2 (Boogaard et al., 2019; Lelieveld et al., 2020). The number of deaths per year is very high, although several countries such as the United States have taken measures (Boogaard et al., 2019). Lelieveld et al. (2020) estimated that 8.8 million deaths are due to air pollution each year. Furthermore, focusing only on all sources of ambient air pollution, they estimated that the life expectancy is decreased by 2.9 years. This is even higher than their estimations for tobacco smoking (2.2 years), HIV/AIDS (0.7 years) and parasitic and vector-borne diseases (0.6 years). It is therefore not surprising that air pollution is suggested to be one of the major, possibly even the leading, global cause of death.

A major air pollutant is particulate matter (PM). This consists of a mixture of particles with many different shapes, chemical compositions, origins, solubility and size (Kelly & Fussell, 2011). Sizes can range from $PM_{0.1}$ consisting of particles with a maximum diameter of 0.1 μm, to PM_{10} with a maximum diameter of 10 μm. In this regard, the smaller the diameter, the deeper the particle can travel in the lungs, or even directly into the bloodstream (Guarnieri & Balmes, 2014; Kampa & Castanas, 2008; Lelieveld et al., 2020). Another trait of PM is that they can transport other pollutants and immunogenic substances with them such as heavy metals. Heavy metals can have toxic effects on humans, even while they are still in the womb (Guarnieri & Balmes, 2014; Kampa & Castanas, 2008; Kelly & Fussell, 2011).

This results in possible negative prenatal effects, such as nervous system impairment (Kampa & Castanas, 2008). Furthermore, studies indicated that the risk of respiratory disease formation in children increases when the mother has been exposed to PM during pregnancy (Kelly & Fussell, 2011; Olsson et al., 2021). One respiratory disease that has been associated with prenatal exposure to air pollution is asthma (Kelly & Fussell, 2011; Olsson et al., 2021). Asthma is an inflammation of the bronchi that can obstruct the in- and outflow of fresh air, leading to shortness of breath (**Appendix A1**; Margelidon-Cozzolino et al., 2022; Trevor & Deshane, 2014). In severe cases, this may lead to hospitalization, cancer and death (Kelly & Fussell, 2011). It is a common disease that has been widespread throughout the world, affecting millions of people (Kampa & Castanas, 2008; Olsson et al., 2021; Trevor & Deshane, 2014).

The precise details on the emergence of asthma are unknown but many studies showed that the environment is playing a role. For example, Olsson et al. (2021) found an increased risk of asthma in the first three years of children in Sweden when exposed to $PM_{2.5}$. Additionally, Achakulwisut et al. (2019) argued that 4.0 million asthma cases in children between 0 and 18 years is due to NO_2 pollution at a 2 parts per billion (pbb) level. This corresponds to 13% of the worldwide incidence (Achakulwisut et al., 2019). At the same time, they argued that higher CO_2 levels are often correlated to higher incidences of asthma as they observed mainly in urban areas with a lot of road traffic.

What dominates studies such as that of Achakulwisut et al. (2019), is that they primarily focus on the effects of air pollution on asthma in urban areas. This does not mean, however, that there are no effects of air pollution in rural areas. The World Health Organization (WHO) advices for recommended daily air pollutants exposure are exceeded in many countries, even those that have taken measures to reduce air pollution (Boogaard et al., 2019). In 2017, over 90% of the world's population exceeded the recommended $PM_{2.5}$ level (Boogaard et al., 2019).

The purpose of this review is therefore to compare the effects of ambient air pollution on asthma development in both urban and rural Europe. By focusing only on ambient air pollution, conclusions can be drawn that apply to everybody, even though there are differences in indoor air pollution. By focusing only on Europe, the differences of indoor air pollution are reduced. In many countries outside Europe, especially in rural areas in low and middle income countries, it is still very common to cook on an open fire; which has a large impact on the respiratory system (Guarnieri & Balmes, 2014; Kelly & Fussell, 2011).

Based on preliminary research about sources of air pollution (**Appendix A2**), it was decided to focus in this review on five pollutants: $PM_{2.5}$, PM_{10}, Nitrogen dioxide (NO_2), Ozone (O_3) and Sulphur dioxide (SO_2). It was hypothesized that the effects of O_3 exposure on asthma occur mainly in rural areas, since

concentrations are higher there. (Guerreiro et al., 2014). In contrast, PM and NO_2 effects on asthma were expected to occur mainly in urban areas because motor vehicle combustion is concentrated in these areas. (European Environment Agency, 2021). The effects of SO_2 are expected to be more difficult to link to rural or urban areas, as its main source is factories that may be present in both rural and urban areas (Guerreiro et al., 2014).

Finally, in order to obtain as complete a picture as possible, both long- and short-term effects of air pollution exposure were examined. For the short-term effects, the main focus was on effects of asthma exacerbation. For long-term effects the main focus was on asthma acquiring. It was hypothesized that effects of both short-term and long-term would be especially strong in urban areas as air pollution concentrations are generally higher there (Guerreiro et al., 2014).

4. METHODS

Literature was searched between October 31 2022 and November 28 2022. Based on the topic, two databases, namely Scopus and PubMed, were selected. Scopus was used as a general database while PubMed served as a more specific medical database. Some articles were also found within citations of other articles.

To find the most useful articles, clear search terms were used in combination with critically scanning through the search results. For the introduction and the appendix section, combinations of the search words 'air pollution', 'air pollutants', 'asthma', 'exposure', 'risk', 'global', 'disease', 'mechanism' and 'th17' were used in Scopus and PubMed.

Since air pollution emissions in Europe decreased a lot since 1990 (European Environment Agency, 2021; Guarnieri & Balmes, 2014), it was chosen to use only papers from the past 15 years (2007-2022). For the result section, due to the research question, only papers focusing on Europe were used. For parts that are more about the general picture, papers around the world were used. Correspondingly, all papers were in English, in their final publication stage and completely open access following the Open Science concept.

In **Figure 1** the selection process for the results sections, chapter five and six, is described. The decision was made to focus on the basic principles of air pollution and their effects on asthma. Therefore, only single-pollutant models were selected and effects of demographics, such as gender, were not considered. If a study investigated multiple models,

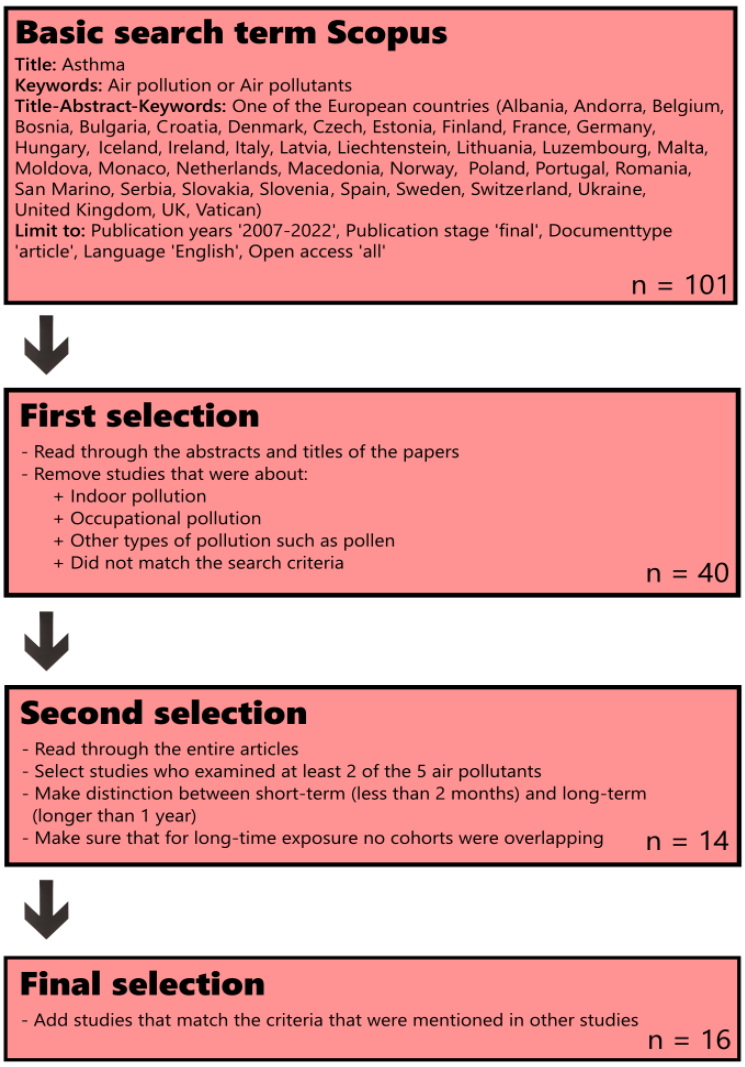

Figure 1- Selection process for short-term and long-term air pollutant exposure papers in relation to asthma disease.

for example univariate vs. multivariate models, the simplest models were included in the result section. In addition, if a study did not mention anything about significance, the 95% interval was considered. If it contained 1.00, it was declared as unsignificant unless the study itself indicated that it was significant. Some studies lacked the raw risk results and only showed figures. In these cases, risks were estimated from the figures. In addition, only effects of particulate matter ($PM_{2.5}$ and PM_{10}), nitrogen dioxide (NO_2), ozone (O_3) and sulfur dioxide (SO_2) on asthma were investigated. This decision was made after an analysis of different sources of air pollution (**Appendix section A1)** showed that these five air pollutants seemed to have a clear role in their effects on asthma in urban and rural areas. In addition, distinction is made between short-term (less than two months of exposure) and long-term exposure (at least 1 year of exposure) articles. For the short-term effects, the main focus was on effects of asthma exacerbation. For long-term effects the main focus was on asthma acquiring. To obtain a broad picture, the choice was made to avoid overlap in population cohorts used in studies. Only for the cohorts of GINIplus and LISAplus an exception was made as these cohorts were found unique in the sense that there was a clear distinction between rural and urban.

5. RESULTS – SHORT-TERM EFFECTS OF POLUTANTS ON ASTHMA

Based on the search strategy, ten studies were included in this section. More details about these studies are summarized in **Table 1**. Of these studies, seven were based on measurements from urban areas, two primarily from urban areas and one from both rural and urban areas. All studies investigated effects of air pollutant exposure based on past exposure measures using a lag period. Lag periods were between 0 and 50 days. In **Figure 2A-E**, effects from different studies are divided by particle.

Particulate matter

PM is included in each study. Overall, all significant results indicated positive associations, meaning that the probability of asthma exacerbation was increased by an increase in PM (**Figure 2A&B**). Small differences have been found between $PM_{2.5}$ and PM_{10}.

Of the ten studies, three studies found very small and similar effects of $PM_{2.5}$ and PM_{10} with odds ratio's (ORs) and risk ratios (RRs) laying around one depending on the number of lag days (Dąbrowiecki et al., 2022; Hoffmann et al., 2022; Santus et al., 2012). Seven studies examined effects of both $PM_{2.5}$ and PM_{10}. Canova et al. (2012), for example, found that in adult hospitalized asthma and/or COPD patients, an increase of 10 $\mu g/m^3$ of $PM_{2.5}$ was associated with an OR of 1.45 (95% CI: 1.12–1.88) at the day of hospitalization (lag 0). An OR of 1.26 (95% CI: 1.04–1.52) was associated with PM_{10} exposure at lag day 0.

Another study that pointed out a higher effect of $PM_{2.5}$ in comparison to PM_{10} is the study of Kovacevic (2020). They investigated the OR to visit the emergency department as an adult due to a 10 $\mu g/m^3$ increase in air pollutant exposure. They found the highest OR of 1.76 (95% CI: 0.74–4.18) for $PM_{2.5}$ exposure with a lag of 3 days. PM_{10} exposure was associated with an OR of 0.92 (95% CI: 0.45–1.87) on lag day 3. A similar pattern was found by Iskander et al. (2011) in which the OR to be hospitalized due to an interquartile range (IQR) increase in air pollution was determined. The highest OR associated with $PM_{2.5}$ was 1.09 (95% CI: 1.04–1.13) at lag 3, while this was 1.07 (95% CI: 1.03–1.10) for PM_{10} at lag 3.

When comparing children, adults and elderly, Halonen et al. (2008) showed that effects of $PM_{2.5}$ can differ among age groups. In their study, it was shown that an IQR increase of $PM_{2.5}$ exposure increased the hospitalization of asthma-COPD children (0-18 years) with 2.56% (95% CI: -0.17–5.36) at lag 4. In contrast, the highest increase in hospitalization for elderly (65+) due to $PM_{2.5}$ exposure was 3.09% (95% CI: 0.95–5.27) at lag 0. In adults (18-65) effects of $PM_{2.5}$ exposure lacked a clear pattern. They argued that effects of PM are delayed in children and more direct in elderly (Halonen et al., 2008).

When comparing rural with urban areas, Fuertes et al. (2015) showed using spirometry research that lung function decreased due to an IQR increase in PM_{10} exposure in a predominantly rural area. They found that the first 50% of the forced expiratory flow (FEF) in adolescents decreased by 77.02% (95%

CI: -151.55–-2.49%). In addition, an IQR increase of $PM_{2.5}$ exposure was associated with a 49.05% (95% CI: -95.59–-2.60%) decrease in FEF_{75}. In contrast, they found no significant effects in the urban area they investigated.

Kowalska et al. (2020) determined the RR of getting hospitalized or visit the hospital caused by an asthma exacerbation due to an IQR increase in $PM_{2.5}$ concentration. Based on the moving average of $PM_{2.5}$ concentrations between the day of admission and 50 days before admission, they found an increase in RR over time. The highest risk was found after 50 days of exposure and the lowest after 1 day of exposure. Furthermore, the risk of getting hospitalized was constantly higher. For example, the RR to be hospitalized was 1.069 (95% CI: 0.981–1.166) at lag 50, while the RR to be visit the hospital was 1.056 (95% CI: 1.016–1.098) at lag 50.

Nitrogen dioxide

NO_2 was also examined by all studies and, just like PM, all the significant results indicated positive associations (**Figure 2E**). In addition, many patterns found for PM exposure match those of NO_2. For example, Canova et al. (2012) showed the highest OR, 1.47 (95% CI: 1.02–2.10), at lag 0. That is not only the highest OR at the same lag but also a very comparable sized risk in comparison to PM results.

Five studies found ORs and RRs varying between 0.91 and 1.10. Comparing these risks over time, there is no consensus about which lag causes the highest risk. Dabrowiecki et al. (2022) and Hoffman et al. (2022) found the highest RRs to be hospitalized of 1.10 (95% CI: 1.08–1.11 and 95% CI: 1.013–1.195) at lag 0. Laurent et al. (2008) found the highest association, an OR of 1.025 (95% CI: 0.990–1.062), also at lag 0. In contrast, Iskander et al. (2011) and Santus et al. (2012) found that ORs to be hospitalized increased by lag day with the peak at lag 4 (1.08; 95% CI: 1.14–1.02 and 1.034; 95% CI: 1.023–1.048). Halonen et al. (2008) showed a similar pattern with a 10.9% (95% CI: 6.38–15.5) risk change in children at lag 4. For the elderly, a reverse pattern was observed with the peak point at lag 0 with a risk change of 4.82% (95% CI: 1.26–8.50). For the adults, there was no clear pattern visible in risk change.

According to the models proposed by Kowalska et al. (2020) an IQR increase of NO_2 was associated with a RR to be hospitalized of 1.365 (95% CI: 1.157–1.611) after 50 days of exposure while the RR to visit the hospital was 1.229 (95% CI: 1.139–1.325). Similar to the results of PM, the RR increased as the exposure time increased.

Fuertes et al. (2015) could not find any significant association between NO_2 exposure and lung function change. When comparing rural with urban areas, no clear patterns were visible.

Ozone

Five studies examined effects of O_3 on asthma. Canova et al. (2012), Hoffman et al. (2022) and Laurent (2008) observed no significant effects. Santus et al. (2012), in contrast, found a very strong effect of ozone. They found that as time of exposure increased, OR increased. The highest OR of 1.781 (95% CI: 1.584–2.002) was found at the cumulative O_3 exposure from days 3 to 5 (lag 3-5; **Figure 2D).**

Fuertes et al. (2015) found that an IQR increase of O_3 exposure was associated with a decrease of 85.39% (95% CI: -165.05–-5.72) in peak expiratory flow (PEF) at lag day 1 in an urban area. In comparison, for a rural area, they found a decrease of 18.81% (95% CI: -110.68–-73.05) per IQR increase of O_3 exposure.

Sulfur dioxide

Four studies examined effects of SO_2 on asthma (**Figure 2C**). However, none of the studies found significant results (Dąbrowiecki et al., 2022; Kovacevic et al., 2020; Laurent et al., 2008; Santus et al., 2012). Most risks were very close to one. The highest OR was found by Kovacevic et al. (2020) who determined the OR to be hospitalized. They determined that an increase of 10 $\mu g/m^3$ in SO_2 exposure was associated with a OR of 1.07 (95% CI: 0.46–2.48) at lag day 1. Dąbrowiecki et al. (2022) and Santus et al. (2012) also investigated effects of SO_2 exposure on hospitalization. They found an overall RR of 1.044 (95% CI: 0.986–1.104) and an OR of 1.059 (95% CI: 0.986–1.137). Laurent et al. (2008) determined the OR to have an asthma attack to be 1.056 (95% CI: 0.979–1.139) at lag day 0-1.

Table 1 – Study details of the selected short-term exposure studies.
OR = odds ratio; RR = relative risk; TSP = total suspended particles; BC = black carbon; SQA = Study Quality Assessment. The Study Quality Assessment was based on guidelines of NHLBI (n.d.). There were 3 types of studies: CC refers to a case-control study; CO refers to a cohort study; NC refers to a study without a control group, also called a retrospective case study. Each study has been ranked and noted as the number of question rated as 'good' or 'fair'/total number of questions. NA refers to the number of questions that were not applicable to the study.

First author, year	Place; Country	Area	Research subjects	N	Result expression	Pollutants	SQA
Canova, 2012	London; United Kingdom	Urban	Hospitalized adult (18+) asthma and/or COPD patients	234	OR to be hospitalized due to a 10 $\mu g/m^3$ increase in pollutant exposure on the day of admission (lag 0) to 3 days before (lag 3)	$PM_{2.5}$ PM_{10} NO_2 O_3	CC; 9/12; 3 NA
Dabrowiecki, 2022	Warsaw, Cracow & Tricity; Poland	Urban	Hospitalized asthma patients (all ages)	31,919	RR to be hospitalized due to a 10 $\mu g/m^3$ increase in pollutant exposure on the day of visit (lag 0) to 6 days before (lag 6)	$PM_{2.5}$ PM_{10} NO_2 SO_2	CC; 7/12; 3 NA
Fuertes, 2015	Munich, Upper Bavaria region and Swabia region; Germany Wesel, Münster region and Düsseldorf region; Germany	Mainly urban Mainly rural	Adolescents (on average 15.2 years) with and without asthma	1274 992	Lung function change before bronchodilation due to an IQR increase in pollutant exposure 1 or 7 days before testing	$PM_{2.5}$ PM_{10} NO_2 O_3	CO; 11/14; 2 NA
Halonen, 2008	Helsinki, Finland	Urban	Hospitalized children (18-) with asthma and/or COPD Hospitalized (15-64) adults with asthma and/or COPD Hospitalized elderly (65+) with asthma and/or COPD	4807 6312 7239	Change in percentage of people getting hospitalized due to an IQR increase in pollutant exposure on the day of admission (lag 0) to 5 days before (lag 5)	$PM_{2.5}$ PM_{10} - $PM_{2.5}$ $PM_{0.03}$ $PM_{0.03\text{-}0.1}$ NO_2 CO	NC; 8/12; 3 NA
Hoffmann, 2022	Berlin, Germany	Urban	Hospitalized asthma patients (18+)	876	RR to be hospitalized due to a 10 $\mu g/m^3$ increase in pollutant exposure on the day of visit (lag 0) to 7 days before (lag 7)	$PM_{2.5}$ PM_{10} NO_2 O_3 O_x	NC; 7/12; 3 NA
Iskandar, 2011	Copenhagen; Denmark	Urban	Hospitalized asthma patients (0-18)	8,226	OR to be hospitalized due to an IQR increase in pollutant exposure on the day of admission (lag 0) to 4 days before (lag 4)	$PM_{2.5}$ PM_{10} $PM_{0.1}$ NO_2 NO_x	CC; 9/12; 3 NA
Kovacevic, 2020	Užice, Čajetina & Kosjerić; Serbia	Urban and rural	People (18+) with allergic asthma who came in contact with the emergency department due to asthma problems	179	OR to visit the emergency department due to a 10 $\mu g/m^3$ increase in pollutant exposure on the day of the visit (lag 0) to 3 days before (lag 3)	$PM_{2.5}$ PM_{10} NO_2 SO_2 BC	CC; 9/12; 3 NA
Kowalska, 2020	Silesian voivodeship, Poland	Mainly urban	Hospitalized asthma patients Outpatient visitors with asthma exacerbation	3815 156,836	RR to have asthma exacerbation of due to IQR increase in pollutant exposure based on the moving average between 1 day and 50 days before.	$PM_{2.5}$ NO_2 NO_x	NC; 8/12; 3 NA
Laurent, 2008	Strasbourg; France	Urban	People (all ages) with asthma attacks who called physicians	4,677	OR to have an asthma attack due to a 10 $\mu g/m^3$ increase in pollutant exposure on the day of the call (lag 0) to 5 days before (lag 5)	PM_{10} NO_2 SO_2 O_3	CC; 9/12; 3 NA
Santus, 2012	Milan; Italy	Urban	People (all ages) with asthma who are admitted to the emergency rooms due to asthma problems	3,569	OR to be admitted to the emergency department due to an increase of 10 $\mu g/m^3$, 5 $\mu g/m^3$, 1 mg/m^3, 2.6 mg/m^3, 4.24 mg/m^3 or 7.96 mg/m^3 pollutant exposure on the day of the admission (lag0) to 5 days before (lag5)	$PM_{2.5}$ PM_{10} NO_2 SO_2 O_3 CO C_6H_6 C_7H_8 C_8H_{10}	CC; 9/12; 3 NA

[A] $PM_{2.5}$

	Canova, 2012	Dabrowiecki, 2022	Halonen, 2008[a]	Halonen, 2008[b]	Halonen, 2008[c]	Iskandar, 2011	Kowalska, 2020[a]	Kowalska, 2020[b]	Kovacevic, 2020	Santus, 2012
Overall		**1.01**				**1.09**				
Lag 0	**1.45**	**1.01**	0.40	1.32	**3.09**	1.04			1.28	0.99
Lag 1	1.08	1.00	-0.06	1.46	**2.26**	**1.05**			1.39	0.99
Lag 2	0.96	0.99	0.41	-0.90	1.91	**1.07**			1.30	1.00
Lag 3	1.09	1.00	2.52	0.67	-0.24	**1.09**			1.76	1.00
Lag 4		**1.00**	2.56	-1.55	0.49	**1.06**				1.00
Lag 5		**1.01**	1.18	-1.79	1.03					1.01
Lag 6		1.01								
Lag 0-1	**1.38**						1.01	1.03		
Lag 0-2										0.99
Lag 0-3	1.40						1.01	1.02		
Lag 3-5										1.08
Lag 0-4										
Lag 0-5							1.02	1.03		
Lag 0-7							1.02	1.05		
Lag 0-14							**1.03**	1.06		
Lag 0-30							**1.05**	1.06		
Lag 0-40							**1.05**	1.06		
Lag 0-50							**1.06**	1.07		

Figure 2A:E - Summary of short-term effects of $PM_{2.5}$ [A], PM_{10} [B], SO_2 [C], O_3 [D], NO_2 [E] on asthma with lag days. *'Overall' indicates that besides the effect per lag day also an overall effects was determined.*

[B] PM_{10}

	Canova, 2012	Dabrowiecki, 2022	Iskandar, 2011	Kovacevic, 2020	Laurent, 2008	Santus, 2012
Overall		**1.01**	**1.07**			
Lag 0	**1.26**	**1.02**	1.02	1.01	1.03	1.00
Lag 1	1.15	0.99	1.04	1.00		1.01
Lag 2	1.15	0.99	**1.04**	0.71		1.01
Lag 3	1.20	1.00	**1.07**	0.92		**1.02**
Lag 4		1.00	1.04			1.02
Lag 5		**1.01**				1.01
Lag 6		1.01				
Lag 0-1	1.25				1.04	
Lag 0-2					1.03	1.01
Lag 0-3	**1.35**				1.02	
Lag 3-5						1.04
Lag 0-4					1.01	
Lag 0-5					1.00	

[C] SO_2

	Laurent, 2008	Dabrowiecki, 2022	Kovacevic, 2020	Santus, 2012
Overall		1.04		
Lag 0	1.05	1.04	0.83	0.98
Lag 1		1.00	1.07	0.98
Lag 2		0.99	1.01	1.06
Lag 3		1.00	0.57	1.04
Lag 4		1.00		1.05
Lag 5		1.01		1.02
Lag 6		1.02		
Lag 0-1	1.06			
Lag 0-2	1.04			1.01
Lag 0-3	1.02			
Lag 3-5				0.97
Lag 0-4	1.01			
Lag 0-5	1.01			

[D] O_3

	Canova, 2012	Laurent, 2008	Santus, 2012
Lag 0	1.13	0.99	1.01
Lag 1	0.89		**1.05**
Lag 2	1.02		**1.05**
Lag 3	0.80		**1.06**
Lag 4			**1.04**
Lag 5			**1.04**
Lag 0-1	0.83	1.00	
Lag 0-2		0.99	**1.07**
Lag 0-3	0.81	1.00	
Lag 3-5			**1.78**
Lag 0-4		1.00	
Lag 0-5		1.00	

[E] NO_2

	Canova, 2012	Dabrowiecki, 2022	Halonen, 2008[a]	Halonen, 2008[b]	Halonen, 2008[c]	Hoffmann, 2022	Iskandar, 2011	Kowalska, 2020[a]	Kowalska, 2020[b]	Kovacevic, 2020	Laurent, 2008	Santus, 2012
Overall		**1.05**					**1.10**					
Lag 0	**1.47**	**1.10**	-0.09	2.69	**4.82**	**1.10**	1.04			1.23	1.03	0.97
Lag 1	1.11	0.98	1.92	-0.44	2.32	0.91	1.04			1.30		0.97
Lag 2	0.99	0.96	3.61	-1.14	2.97	0.97	1.05			0.70		1.00
Lag 3	1.23	0.97	**4.53**	2.81	-0.09	0.96	**1.07**			1.00		1.01
Lag 4		0.99	**10.9**	0.59	-0.88	1.01	**1.08**					**1.03**
Lag 5		**1.01**	**9.36**	**3.70**	1.44	0.96						**1.02**
Lag 6		**1.05**				1.08						
Lag 7						1.05						
Lag 0-1								**1.05**	**1.19**		1.02	
Lag 0-2											1.02	0.97
Lag 0-3	1.52							**1.04**	**1.09**		1.01	
Lag 3-5												0.98
Lag 0-4											1.01	
Lag 0-5								**1.07**	1.08		1.01	
Lag 0-7								**1.08**	**1.12**			
Lag 0-14								**1.13**	**1.18**			
Lag 0-30								**1.18**	**1.25**			
Lag 0-40								**1.20**	**1.26**			
Lag 0-50								**1.23**	**1.37**			

6. RESULTS - LONG-TERM EFFECTS OF POLUTANTS ON ASTHMA

In this result section, seven studies were included. More details about these studies are summarized in **Table 2**. Of these studies, four included both urban as rural sites while three were only focused on urban sites.

Particulate matter

All studies investigated the effects of PM exposure on asthma development. Divided into PM_{10} and $PM_{2.5}$, six studies investigated PM_{10} and five studies investigated $PM_{2.5}$.

Of these studies, two did not find significant associations for either PM_{10} or $PM_{2.5}$. Yet, most of the associations they found were positive risks. Nordeide Kuiper et al. (2021) found, for example, that the OR to have allergic asthma in children was 1.04 (95% CI: 0.98–1.11) based on PM_{10} exposure from birth until diagnosis. In comparison, they found an OR of 1.02 (95% CI: 0.98–1.07) associated with $PM_{2.5}$ exposure. Additionally, they investigated the OR to have an asthma attack in the last year. After a lifetime exposure, the OR was 1.19 (95% CI: 0.75–1.91) for $PM_{2.5}$ exposure and 1.45 (95% CI: 0.89–2.38) for PM_{10} exposure. Furthermore, Nordeide Kuiper et al. (2021) investigated the risk to have a lower lung function using forced expiratory volume (FEV) and forced vital capacity (FVC). The highest OR in this part of their study associated with PM exposure was an OR of 2.43 (95% CI: 0.64–9.91) for $PM_{2.5}$ exposure. In comparison, an OR of 1.85 (95% CI: 0.43–7.91) was found for PM_{10} exposure.

Mölter et al. (2015) investigated the OR to have asthma at either age 4/5 or age 8/10. At age 4/5, $PM_{2.5}$ and PM_{10} exposure was associated with positive effects on having asthma (OR: 0.76 (95% CI: 0.43–7.91) for $PM_{2.5}$; OR: 0.78 (95% CI: 0.50–1.20) for PM_{10}). In contrast, at age 8/10, these effects were negative. $PM_{2.5}$ exposure was associated with an OR of 1.13 (95% CI: 0.61–2.09) and PM_{10} exposure was associated with an OR of 1.20 (95% CI: 0.64–2.24).

Fuertes et al. (2015) also did not find any general significant effects of PM_{10} or $PM_{2.5}$ exposure on lung function. In their study they investigated effects of 15 years of pollutant exposure on different variables that determine lung function. Besides general effects, they also distinguished between effects in a mainly rural and a mainly urban area. Here, differences were visible. For example, the FVC was associated with an increase of 34.89 ml (95% CI: 9.37–60.41) in lung capacity per increased IQR urban $PM_{2.5\ mass}$ exposure. In comparison, a decrease of -15.48 ml (95% CI: -50.83–19.87) in FVC was determined in the rural area. Fuertes et al. (2015) additionally looked at the differences between effects of air pollutants on lung function variables in asthmatics and non-asthmatics. In this case, both asthmatics as non-asthmatics showed an increase in FVC for $PM_{10\ mass}$, $PM_{2.5\ mass}$ and $PM_{2.5\ absorbance}$. Effects in asthmatics were however larger. Other lung function variables, such as FEF, showed a similar trend. Yet, in these cases, an IQR increase in any PM exposure was associated with a decrease in lung function.

Alasauskas et al. (2020) and Pénard-Morand et al. (2010) both looked at effects in schoolchildren but with differences in exposure time. Alasauskas et al. (2020) showed that PM_{10} and $PM_{2.5}$ exposure for 1 year was associated with positive ORs to have asthma of 1.012 (95% CI: 1.003–1.021) and 1.037 (95% CI: 1.010–1.064). Of the 51,235 children between 7 and 17 years that were investigated, 3065 children had asthma, which is almost 6%. In the study of Pénard-Morand et al. (2010), the prevalence of lifetime asthma was 10%. In their study distinction was made between how long children lived at the same house address in the periods 3 years, 8 years and lifetime. In the period of 3 years, the OR to have lifetime asthma was 1.28 (95% CI: 1.06–1.51) for PM_{10}. Living 8 years at the same address was associated with an OR of 1.37 (95% CI: 1.02–1.36) and lifetime living at the same address with an OR of 1.36 (95% CI: 1.00–2.00).

Cai et al. (2015) and Liu et al (2021) both looked at a mixed adult population living at rural and urban sites. In these studies, the prevalence of having asthma was 4% and 2%. Liu et al. (2021) investigated the hazard risk (HR) to develop adult-onset asthma after pollutant exposure based on data from 16.6 years. For $PM_{2.5}$ exposure, they found a positive HR of 1.24 (95% CI: 1.06–1.45). Cai et al. (2015) investigated, on the other hand, the OR to either ever-had asthma or to currently have asthma after pollutant exposure. Based on data from 7-8 years, they found that PM_{10} exposure was associated with a positive OR for both asthma incidences. The OR's were 1.145 (95% CI: 1.112–1.179) and 1.063 (95% CI: 1.012–1.115).

Nitrogen dioxide

Effects of NO_2 on asthma development were examined by all studies. Similar to the short-term effects, the outcomes of NO_2 are comparable to those of PM. Mölter et al. (2015) did not find any significant association between NO_2 exposure and having asthma. However, there are some differences visible between the different cohorts they investigated. The PIAMA and MAAS cohort were associated with a positive OR of 1.26 (95% CI: 1.02–1.55) and 4.20 (95% CI: 1.31–13.42) for NO_2 exposure at the birth address at the age of 8 years. In contrast the BAMSE and GINI and LISA plus cohorts were never associated with significant risks. In the study of Fuertes et al. (2015), in which the cohorts GINIplus and LISAplus also were investigated, no significant results were found. Yet, when comparing the effects of NO_2 exposure in the rural and urban areas studied, the effects on lung function variables were mainly negative in the urban area and mostly positive in the rural area. When comparing lung function variables of asthmatics with non-asthmatics, mostly negative associations were found and the effects were stronger for asthmatics (Fuertes et al., 2015).

In contrast to PM, Pénard-Morand et al. (2010) could not find significant associations between NO_2 exposure and (last year) asthma development in children. Alasauskas et al. (2020), on the other hand, did find a significant OR of 1.165 (95% CI: 1.005–1.027) to have asthma as a child based on 1 year of NO_2 exposure.

Nordeide Kuiper et al. (2021) investigated a cohort consisting of people with an average age of 28.2 years. They investigated the OR to be diagnosed with asthma by a physician, to have allergic asthma and to have non-allergic asthma per increase of 10 $\mu g/m^3$ NO_2 exposure. The OR to have physician diagnosed asthma was 1.01 (95% CI: 1.00–1.03) while this was 1.02 (95% CI: 1.00–1.04) for allergic asthma. The OR of having non-allergic asthma was non-significant. In addition, they also examined the OR to have an asthma attack in the last 12 months and the OR to have a lung function below normal levels for three different periods: 0-10 years, 10-18 years and lifetime. Associations between NO_2 exposure and having an asthma attack were not significant, yet all positive. Associations between NO_2 exposure and lung function were not significant, yet all below 1. This would indicate that NO_2 exposure enhances the lung function.

Cai et al. (2015) and Liu et al (2021) found positive significant associations between NO_2 exposure and having adult asthma. Liu et al. (2021) found a HR of 1.19 (95% CI: 1.11–1.25) for asthma incidence. Cai et al. (2015) found an OR of 1.025 (95% CI: 1.017–1.033) to ever-have asthma. In contrast to PM results, no significant association was found between NO_2 exposure and current asthma (OR: 0.991 (95% CI: 0.978–1.004)).

Ozone

Three studies investigated the effects of long-term ozone exposure on asthma development. Two of these studies found significant positive associations.

Liu et al. (2021) determined that an increase of 10 $\mu g/m^3$ O_3 exposure was associated with a asthma incidence hazard ratio (HR) of 0.89 (95% CI: 0.81–0.98). Nordeide Kuiper et al. (2021) investigated the OR to be asthma diagnosed by a physician from birth until diagnosis. They found that with a 10 $\mu g/m^3$ increase of O_3 exposure the OR was 0.95 (95% CI: 0.91–0.98). Associations between O_3 and having an asthma attack were not significant. Yet, all of them were positive associations. Associations between O_3 and lung function were all significant positive. The highest OR was 4.23 (95% CI: 1.60–11.17) for forced vital capacity (FVC) in the first 10 years of a life.

Fuertes et al. (2015) did not find any significant associations between lung function variables and O_3 exposure. Yet, they showed clear differences between asthmatics and non-asthmatics. Whereas the associations of O_3 on non-asthmatics were very small, they were clearly larger on asthmatics. Differences between urban and rural areas were not clear. For example, whereas urban O_3 exposure was associated with an 17.76% (95% CI: -11.11–46.64) increase in FVC and an 7.61% (95% CI: -54.51–69.74) increase in FEF_{50}, rural O_3 exposure was associated with a 18.14% (95% CI: -78.34–42.06) decrease in FVC and an 0.75% (95% CI: -126.98–128.47) increase in FEF_{50}.

Sulfur dioxide

Two studies investigated the effects of SO_2 exposure on asthma development in children. Alasauskas et al. (2020), who investigated having asthma after 1 year of SO_2 exposure, did not find a significant association. Pénard-Morand et al. (2010), that investigated children who lived at least 3 years in the same house, did found an effect. They found that, based on an IQR increase of SO_2 exposure, the OR to have exercise-induced asthma is 1.27 (95% CI: 1.11–1.53). In addition, they also examined the OR to have asthma in the last year, being 1.29 (95% CI: 1.03–1.71), and to have lifetime asthma, being 1.26 (95% CI: 1.11–1.42). To further examine the effect of long-term exposure, the OR of having lifetime asthma was also examined for children living 8 years and throughout lived in the same house. Taking the average of these years, they examined an OR of 1.33 (95% CI: 1.01–1.89) for eight years and 1.38 (95% CI: 0.95–1.92) for lifetime.

Table 2- The Study Quality Assessment was based on guidelines of National Hearth Lung and Blood Institute (2021).
There were 3 types of studies: CC refers to a case-control study; CO refers to a cohort study; NC refers to a study without a control group, also called a retrospective case study. Each study has been ranked and noted as the number of question rated as 'good' or 'fair'/total number of questions. NA refers to the number of questions that were not applicable to the study.

First author, year	Cohorts	Place; Country	Area	Research subjects	N	Duration	Result expression	Pollutants	SQA
Alasauskas; 2020	-	Vilnius; Lithuania	Urban	Schoolchildren (7-17 year)	51,235	1 year	OR of having asthma due to air pollutant exposure	$PM_{10\ mass}$ $PM_{2.5\ mass}$ $PM_{2.5\ absorbance}$ NO_2 SO_2 CO Benzop[a]pyrene	CO; 10/14; 3 NA
Cai, 2015	HUNT3, LIFELINES & UK BIOBANK	Nord-Trøndelag County; Norway Friesland, Groningen & Drenthe; the Netherlands Criss-crossing the country; United Kingdom	Urban and rural Rural Urban and rural	Adults (20-69 years)	646,731	7-8 years	Odds ratio (OR) to either have or had asthma per 10 $\mu g/m^3$ pollutant exposure	PM_{10} NO_2	CO; 8/14; 3 NA
Fuertes, 2015	LISAPLUS & GINIPLUS	Munich, Upper Bavaria region and Swabia region; Germany Wesel, Münster region and Düsseldorf region; Germany	Mainly urban Mainly rural	Adolescents (on average 15.2 years) with and without asthma	2,266	15 years	Lung function change due to an IQR increase of pollutant concentration before and after bronchodilation.	PM_{10} $PM_{2.5}$ NO_2 O_3	CO; 11/14; 2 NA
Liu, 2021	CEANS, SDPP, SIXTY, SALT, SNAC-K, DCH &, DNC	Stockholm (county); Sweden Copenhagen & Aarhus; Denmark	Urban and rural	Adults (on average 55.8 years)	98,326	16.6 years	Hazard risk to develop asthma	$PM_{2.5}$ NO_2 O_3 BC	CO; 10/14; 3 NA
Nordeide Kuiper, 2021	RHINESSA	Bergen; Norway Umea, Uppsala & Gothenburg; Sweden	Urban	People born after 1975 (on average 28.2 years)	3,428	8 and 10 years and lifelong	OR to have non-allergic, allergic or physician diagnosed asthma from birth until diagnosis due to an increase of 1 or 10 $\mu g/m^3$ of pollutant exposure	PM_{10} $PM_{2.5}$ NO_2 O_3 BC	CO; 9/14; 3 NA

							OR to have an asthma attack in the last 12 months due to an increase of 1 or 10 $\mu g/m^3$ of pollutant exposure OR association between lung function and an increase of 1 or 10 $\mu g/m^3$ of pollutant exposure		
Mölter, 2015	GINIplus, LISAplus, BAMSE, PIAMA, & MAAS	Wessel region; Germany Munich region; Germany Stockholm county; Sweden Northern, middle and southwestern part; the Netherlands Great Manchester; United Kingdom	Mainly rural Mainly urban Mainly urban Urban and rural Mainly urban	Children	7096–11 555	4 or 5 and 8 or 10 years	OR to have asthma due to an increase of 10 or 5 $\mu g/m^3$ in pollutant exposure	PM_{10} $PM_{2.5}$ $PM_{2.5\ absorbance}$ NO_2 NO_x	CO; 8/14; 3 NA
Pénard-Morand, 2010	-	Bordeaux, Reims, Strasbourg, Créteil, Clermont-Ferrand & Marseille; France	Urban	Schoolchildren (on average 10.4 years)	2213-4907	3 and 8 years and lifelong	OR of having exercised-induced asthma due to an IQR increase of pollutant exposure OR to have asthma in the last 12 months due to an IQR increase of pollutant exposure OR to have lifelong asthma due to an IQR increase of pollutant exposure	PM_{10} NO_2 NO_x SO_2 CO C_6H_6 VOC	CO; 10/14; 3 NA

7. DISCUSSION

This literature review examined short and long-term effects of five air pollutants ($PM_{2.5}$, PM_{10}, NO_2, O_3 and SO_2) on asthma in rural and urban areas in Europe. Based on 16 studies, it can be concluded that there is a lack of research on the difference between rural and urban areas in Europe. Of the four studies that did include subjects from rural sites, only Fuertes et al. (2015) made a clear distinction between effects of living in rural and urban areas in their results.

It was hypothesized that effects of PM and NO_2 are associated with urban areas while effects of O_3 are associated with rural areas (based on information in **Appendix A2**). SO_2 could be associated with both urban and rural areas. Based on the results, the hypothesis can be partly accepted, as will be discussed now.

Table 3. Summary of effects found by Fuertes et al. (2015) divided per pollutant, exposure duration and landscape type.
Fuertes et al. (2015) has examined effects of air pollutants on eight lung function variables. The table describes the extent to which these variables are overall positive or negative. For example, [--] indicates that the effect of an air pollutant on most of the lung variables is associated with a negative effect. [+/-] indicates that effects were neither positive, nor negative. [X] indicates it was not examined.

	Short-term		Long-term	
	Rural	Urban	Rural	Urban
$PM_{2.5\ absorbance}$	X	X	+	+
$PM_{2.5\ mass}$	--	-	++	--
$PM_{10\ mass}$	--	-	+	--
$NO_{2\ mass}$	++	++	++	--
O_3	-	---	+/-	++

Table 4. Summary of effects found by all studies except Fuertes et al. (2015).
*Ntot indicates the number of studies; Nsig indicates the number of studies that found a significant effect; Nneg indicates the number of studies that found a significant adverse effect on asthma development or asthma exacerbation; Npos indicates the number of studies that found a significant advantageous effect on asthma development or asthma exacerbation; * indicates a study that both found adverse and advantageous effects.*

	Short-term				Long-term			
	N_{tot}	N_{sig}	N_{neg}	N_{pos}	N_{tot}	N_{sig}	N_{neg}	N_{pos}
$PM_{2.5\ mass}$	8	6	6	0	4	2	2	0
$PM_{10\ mass}$	8	6	6	0	5	3	3	0
$NO_{2\ mass}$	9	7	7	0	6	5	5	0
O_3	4	1	1	0	2	1	1*	1*
SO_2	4	0	0	0	2	1	1	0

Effects in rural and urban areas

Fuertes et al. (2015) was able to show some associations between air pollutant exposure and changes in lung function variables after bronchodilation, although few of these were significant. In **Table 3**, these associations are summarized. These results show some clear differences between short-term and long-term effects in rural and urban areas. The effects of PM, NO_2 and O_3 exposure on the long-term are in agreement with the hypothesis. However, on the short-term, they are not. O_3 exposure has a stronger effect in urban areas while PM and NO_2 have a stronger effect in rural areas. It is unclear as to why this trend is apparent. Fuertes et al. (2015) mentioned that these results should be viewed with caution since the short-term exposure monitoring stations of both rural and urban were located in suburban areas. The distinction between pollutant exposure in rural and urban is therefore harder to make.

Effects of PM and NO_2

When looking at the other studies, **Table 4**, which were predominantly focusing on urban areas, effects of PM and NO_2 exposure were negative on both short- and long-term. Additionally, the results showed that effects of $PM_{2.5}$, PM_{10} and NO_2 exposure were similar in risk size and in terms of lag patterns on the short-term. Canova et al. (2012) showed the highest OR to be hospitalized was 1.47 (95% CI: 1.02–2.10) at lag 0 for NO_2, 1.45 (95% CI: 1.12–1.88) at lag 0 for $PM_{2.5}$ and 1.26 (95% CI: 1.04–1.52) at lag 0 for PM_{10}. This example also shows that when comparing $PM_{2.5}$ with PM_{10}, $PM_{2.5}$ seems to have a slightly stronger effect on asthma.

This can be explained by the principle that the smaller particles can travel deeper into the lungs and cause more damage (Guarnieri & Balmes, 2014; Kampa & Castanas, 2008; Lelieveld et al., 2020). Halonen et al. (2008) confirmed this principle by demonstrating that particles smaller than 0.1 μm are associated with stronger effects than $PM_{2.5}$ and PM_{10}. For example, in elderly, the change in hospital emergency room visits due to $PM_{0.01}$ exposure was 4.49% (95% CI: 1.70–7.36), while this was 3.09% (95% CI: 0.95–5.27) for $PM_{2.5}$ and 2.45% (95% CI: 0.18–4.76) for $PM_{10\text{-}2.5}$ at lag 0.

Khreis et al. (2017) found in their meta-analysis the opposite effect. PM_{10} exposure was associated with a OR of 1.05 (95% CI: 1.02–1.08) while an OR of 1.03 (95% CI: 1.01–1.05) was found for $PM_{2.5}$. This indicates that there is still some disagreement. It might be that the composition of PM is of more importance than the size, especially, when considering the small differences between OR. The composition of PM can differ quite a bit in terms of amounts of heavy metals, dust, droplets, smoke and other particles (Kampa & Castanas, 2008). Future research should look further into this.

Effects of O_3 and SO_2

The effects of O_3 and SO_2 exposure on asthma seem not as convincing as for PM and NO_2. Of the four studies that investigated short-term effects of O_3 on asthma, only one found a significant effect (Santus et al., 2012). In addition, effects of long-term O_3 were unclear. Nordeide Kuiper et al. (2021) found mixed results within the same study. While the OR for physician diagnosed asthma due to O_3 exposure was 0.95 (95% CI: 0.91–0.98), the OR to have a lower limit of FVC in the first ten years of child's life was 4.23 (95% CI: 1.60–11.17). This might indicate that impairment of the lungs due to O_3 exposure is not directly related to asthma diagnosis or having an asthma attack. Nordeide Kuiper et al. (2021) argued that O_3 exposure might be mainly associated with a decrease in lung volume and less with obstructive effects. Crisford et al. (2021), on the other hand, suggested another mechanism. They argued that O_3 causes airway inflammations due to neutrophil activation. Activation of neutrophils induces obstructive effects due to mucus hypersecretion and bronchodilation as shown in **Figure A1** (Crisford et al., 2021).

Similar to O_3, the short-term effects of SO_2 on asthma exacerbations were not conclusive. None of the four studies that investigated effects of SO_2 found significant results. The long-term effects of SO_2 on asthma incidence were examined by two studies of which one found significant results. Pénard-Morand et al. (2010) determined that the chance to have life-time asthma as a child increased when the SO_2 exposure time increased. After one year at the same address, SO_2 exposure was associated with a OR of 1.26 (95% CI: 1.11–1.42). After three years, this was associated with an OR of 1.33 (95% CI: 1.01–1.89) and after eight years with an OR of 1.38 (95% CI: 0.95–1.92). The fact that they found a similar trend for PM_{10} indicates that there are differences within the long term, especially when people continue to live in the same place.

The reason Pénard-Morand et al. (2010) was the only study to find significant effects of SO_2 could have several reasons. First, it could be that SO_2 effects are mainly strong in children as Sims et al. (2020) argued. Of the six studies that investigated SO_2, four are performed with mainly adult objects. Furthermore, the main of SO_2 is the industrial sector which is very dependent on the residential location (**Appendix A2;** Guerreiro et al., 2014).

Limitations

This review has several limitations, which will now be discussed. First of all, the effects of air pollution exposure in children and adults seem to differ. For example, Halonen et al. (2008) showed that effects of air pollutant exposure might be more direct in elderly and more delayed in children. Whereas $PM_{2.5}$ exposure caused the highest change in hospitalization for elderly at lag day 0 (3.09%; 95% CI: 0.95–5.27), the highest change for children was found at lag day 4 (2.56%; 95% CI: -0.17–5.36). In addition, the results showed that there are differences in asthma prevalence between adults and children. In the studies of Cai et al. (2015) and Liu et al. (2021) in which adult populations are investigated, the found prevalence was 4% and 2% respectively. In contrast, Alasauskas et al. (2020) and Pénard-Morand et al. (2010) who investigated schoolchildren found prevalence's of 6 and 10%. Two facts might explain these differences. Firstly, due to the shorter length and smaller diameter of the lungs, pediatric lungs are more vulnerable for air pollutants

(Alasauskas et al., 2020). And secondly, the fact that pediatric lungs are still in development means that there is a chance to overcome asthma symptoms later in life (Khreis et al., 2017).

Another limitation is of this literature review is that only single pollutant models were included in the results, while air pollution is actually always a mix of multiple pollutants. Several papers also showed that air pollutants are positively correlated with each other (Alasauskas et al., 2020; Fuertes et al., 2015; Kovacevic et al., 2020; Kowalska et al., 2020). In particular, $PM_{2.5}$ and PM_{10} and NO_2 are often correlated. Moreover, due to their nature, NO_2 and O_3 are correlated as they can be derived from each other (Kelly & Fussell, 2011). Khreis et al. (2017) therefore mentioned that it is actually impossible to link risk effects to individual pollutants. Yet, when considering the results of this review with respect to individual pollutants, it becomes clear that these correlations are also visible in the individual results. Canova et al., (2012) showed that effects of $PM_{2.5}$, PM_{10} and NO_2 exposure were similar in risk size and in terms of lag patterns. Furthermore, Fuertes et al. (2015) showed that, when effects of O_3 were negative, effects of NO_2 were positive which could indicate that they are inversely related (**Table 3**). Nevertheless, more attention should be paid to multipollutant models.

Finally, this review focused only on the overall effects of air pollutants on people with demographic differences not being considered. It has been shown that certain genes, smoking cigarettes, obesity, lower educational level, lower income, stress, non-Caucasian race, and high allergen levels are associated with an increased risk to develop or worsen asthma (Canova et al., 2012; Crisford et al., 2021; Guarnieri & Balmes, 2014; Laurent et al., 2008; Olsson et al., 2021; Santus et al., 2012).

Conclusion

Overall, it can be concluded that the number of studies distinguishing between rural and urban areas in research on the effects of air pollution on asthma is limited. The expectation that PM and NO_2 would have effects mainly in urban areas and O_3 in rural areas was only confirmed for long-term exposure. Other results showed that PM and NO_2 have the clearest effects on asthma, both on the long- and short-term. The difference between effects of $PM_{2.5}$ and PM_{10} exposure is, however, debatable. In future research, it is recommended to focus on multi-pollutant models and include demographic differences such as age.

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APPENDIX

A1 Asthma mechanisms

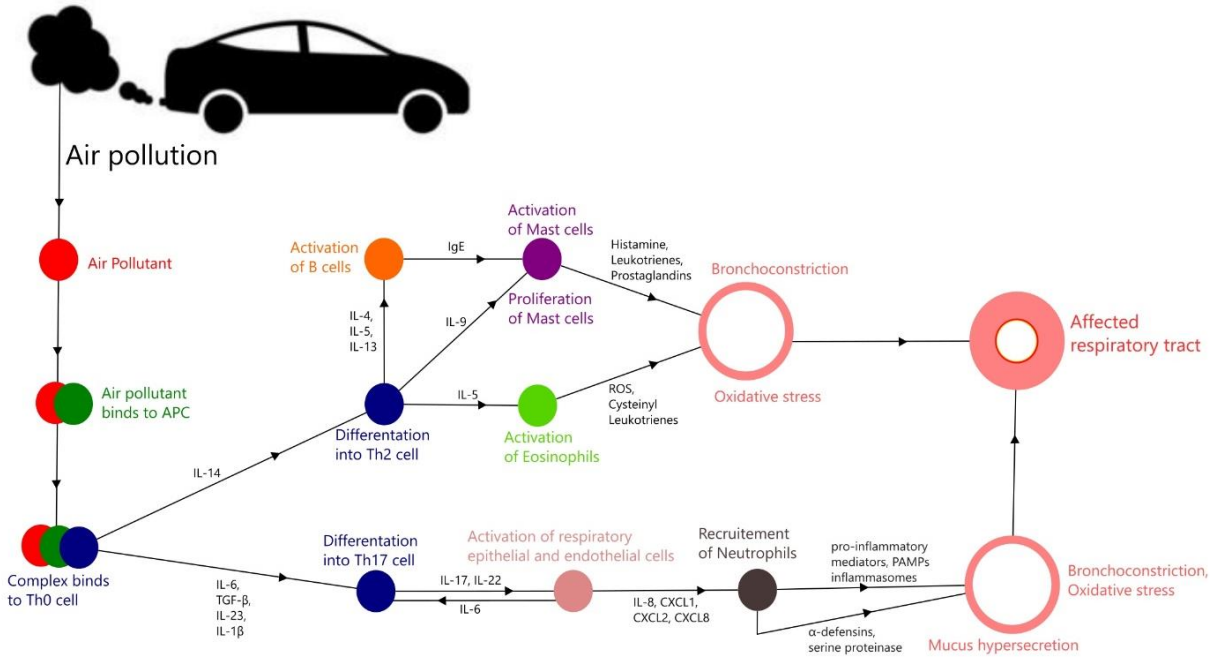

Figure A1- Overview of mechanisms that take place after exposure to an air pollutant and lead to asthmatic reactions. APC = Antigen presenting cell*. Th cell = T-helper cell; IL = interleukin; TGF = transforming growth factor; ROS = reactive oxygen species; CXCL = chemokine ligand with C-X-C motif; PAMPs = pathogen-associated molecular pattern.*

Asthma is an inflammation of the bronchi that can obstruct the in- and outflow of fresh air. The airflow obstruction is due to bronchoconstriction. Induction of bronchoconstriction in people with asthma occurs after activation of an immunological pathway. Activation of this pathway is due a stimulus that has been inhaled such as an air pollutant (Margelidon-Cozzolino et al., 2022; Trevor & Deshane, 2014). For people with severe asthma, exposure to stimulus can cause severe reactions, so called asthma attacks, which may lead to hospitalization (Kelly & Fussell, 2011).

Figure A1 shows two pathways that can be activated after exposure to a stimulus. It starts with an air pollutant that binds to an antigen presenting cell (APC) that subsequently binds to a T-helper (Th) cell. It can then either differentiate in Th2 or Th17, depending on the cytokines. It is possible for both pathways to occur at the same time. However, the Th2/Th17 ratio can differ (Guarnieri & Balmes, 2014; Margelidon-Cozzolino et al., 2022; Trevor & Deshane, 2014).

$T2^{high}$ asthma

Differentiation into Th2 is described in the upper pathway, the '$T2^{high}$ asthma' type. This is the best known type of asthma and has a pathway which is similar to allergic pathways. When T-helper (Th) 2 cells are formed, eosinophils and B cells are activated via expression of different interleukins (IL), namely IL-4, IL-5 and IL-13. B cells subsequently activate mast cells with immunoglobulin (Ig) E. By expression of different cytokines by eosinophils and mast cells, including histamine, smooth muscle tissue in the bronchi is stimulated to constrict and oxidative stress is induced (Hudey et al., 2020; Trevor & Deshane, 2014).

Oxidative stress is a misbalance of free radicals which can induce inflammation. In case of a long-term inflammation, this can cause cancer (Canova et al., 2012; Kampa & Castanas, 2008). In less extreme cases, inflammation in the airways is characterized with coughing, wheezing and shortness of breath (Kelly & Fussell, 2011; Kowalska et al., 2020).

$T2^{low}$ asthma

The bottom pathway is another pathway which relies on the differentiation from Th0 to Th17. This type of asthma is also called 'non-type 2 asthma' or '$T2^{low}$ asthma'(Crisford et al., 2021; Hudey et al., 2020; Margelidon-Cozzolino et al., 2022). Instead of eosinophils, neutrophils play a key role in this type of asthma. In some cases, when the concentration of neutrophils in the sputum is higher than 50%, it is even referred to as 'neutrophilic asthma'. In comparison to $T2^{high}$ asthma, it is a less known type of asthma whose mechanisms to date are still under investigation (Hudey et al., 2020; Margelidon-Cozzolino et al., 2022).

It starts with differentiation of Th17 which is induced by IL-6, TGF-β and IL-1 and stabilized by IL-23 (Margelidon-Cozzolino et al., 2022). Thereafter, Th17 expresses IL-17 and IL-22. Originally only IL-17 was mentioned but the importance of IL-22 is increasingly mentioned in the last decade. The mechanisms of IL-22 are still uncertain but Margelidon-Cozzolino et al. (2022) mentioned that together with IL-17, IL-22 stimulates respiratory epithelial and endothelial cells. These cells subsequently express all kinds of cytokines to stimulate neutrophilic action. An indirect way is by causing a positive feedback loop in which expression of IL-6 stimulates more Th0 cells to differentiate into Th1. Furthermore, they express a wide variety of cytokines that directly recruit neutrophils. (Hudey et al., 2020; Margelidon-Cozzolino et al., 2022; Trevor & Deshane, 2014).

Normally neutrophils use one or multiple of the following methods to kill pathogens: phagocytosis with internal reactive oxygen species (ROS) and other killing enzymes, degranulation with extracellular ROS and proteolytic enzymes or with neutrophil extracellular traps (NETs). In case of asthma, it seems however that all of these methods are altered. There seems to be an increase in NET formation and furthermore there is an increased expression of serine proteases and α-defensins and other pro-inflammatory mediators. This causes bronchoconstriction, oxidative stress and increased mucus production (Crisford et al., 2021).

A2 Ambient Air pollutants

In order to understand the differences between urban and rural air pollution, it is necessary to understand which air pollutants there are and where they come from. In this chapter, air pollutant categories and sources of air pollution are explained.

Air pollutant categories

A way to distinguish air pollutants is by their formation. Air pollutants that are directly emitted in the atmosphere are called primary pollutants. Secondary pollutants, on the other hand, are formed out of other pollutants (European Environment Agency, 2021; Singh & Sharma, 2018). An example of a secondary pollutant is ozone (O_3). Ozone is formed in the lower layers of the atmosphere under influence of the sun by a reaction of nitrogen oxides (NO_x) with volatile organic compounds (VOCs) (European Environment Agency, 2021; Kampa & Castanas, 2008; Kelly & Fussell, 2011; Singh & Sharma, 2018).

Another way to distinguish air pollutants is according to the distinction of Kampa & Castanas (2008) as described in **Table 1**. They separate pollutants in four categories, each consisting of multiple particles that have their own characteristics and origins.

- Particulate matter (PM) consists of mixtures of particles originating from natural and anthropogenic sources. The size of the particulate matter defines the name. PM_{10}, for example, refers to a mixture of particles with a size smaller than 10 µm. Based on the size, there are subcategories defined. PM_{10} and $PM_{2.5}$ are 'coarse particles' with a diameter larger than 1 µm, $PM_{1.0}$ is a 'fine particle' and $PM_{0.1}$ is an 'ultrafine' particle. (Kampa & Castanas, 2008; Singh & Sharma, 2018).
- Gaseous pollutants are a diverse group, including a wide range of different gases commonly found in the atmosphere. Besides natural sources, some arise from the (incomplete) combustion of fossil fuels such as carbon monoxide (CO) and sulfur dioxide (SO_2). In addition, the group includes the subgroup volatile organic compounds (VOCs) which includes, among others, benzene and methane (Kampa & Castanas, 2008). Other examples belonging to gaseous pollutants can be found in **Table A1**.
- Heavy metals consist of components that naturally occur and can never be destroyed, only transported. Transmission towards humans can take place via food, water and air (with PM particles). For a healthy metabolism, a certain intake of heavy metals is necessary for humans. Yet, if they accumulate in the human body, they can be toxic (Guerreiro et al., 2014; Kampa & Castanas, 2008).
- Persistent organic pollutants are similar to heavy metals but are able to degrade on the long term. This group includes chemicals formed undesirably by (incomplete) combustion, for example the burning of plastics or desired by factories to avoid pests. Often they are water insoluble but their ability to bind fats allows them to accumulate in humans (Kampa & Castanas, 2008).

Table A1- Overview of ambient air pollutants in categories.

Particulate matter	Gaseous pollutants	Heavy metals	Persistent organic pollutants
-PM_{10} -$PM_{2.5}$ -$PM_{1.0}$ -$PM_{0.1}$	-Nitrogen oxide (NO) -Nitrogen dioxide (NO_2) -Ozone (O_3) -Carbon monoxide (CO) -Carbon dioxide (CO_2) -Sulfur dioxide (SO_2) -Volatile organic compounds (VOCs) including benzene (C_6H_6) and methane (CH_4)	-Lead -Vanadium -Cadmium -Chromium -Mercury -Manganese	-Furans -Polychlorinated biphenyls (PCB) -Polychlorinated dibenzo-dioxins (PCDDs) -Polychlorinated dibenzo-furans (PCDFs) -Persistent organic pollutants (POPs) including pesticides and fungicides

Sources of air pollutants

Air pollutants can arise from both natural sources and anthropogenic sources or a combination of both. The proportion of anthropogenic sources, however, is larger (Kampa & Castanas, 2008). Based on the report of European Environment Agency (2021), four main anthropogenic sources have been identified and described (**Figure A2**). This does not mean that there are no other sources, but giving a detailed description of them is not the purpose of this review.

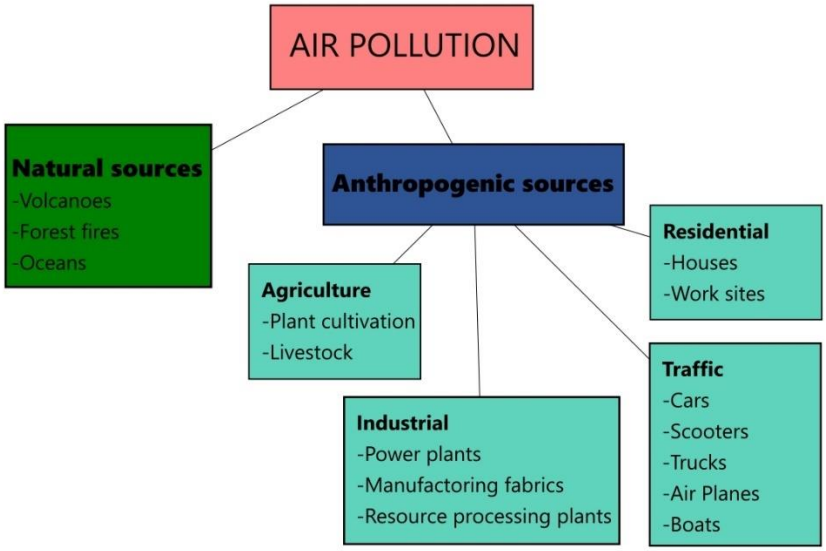

Figure A2- Overview of air pollution sources.

Natural sources

Before explaining more about the anthropogenic sources, some explanation about natural sources. One enormous sized natural source is water. Pollutants emitted by oceans, rivers and other water sources include SO_2 and CO_2 among others (Bertora et al., 2010; Guarnieri & Balmes, 2014; Kampa & Castanas, 2008). In addition, as part of the nitrogen cycle, water stores nitrogen in the form of nitrogen acid (Bertora et al., 2010). As a consequence, oceans emit nitrogen oxides such as N_2O (Bertora et al., 2010).

Two examples of natural sources that are related to natural disasters are volcano eruptions and forest fires. Eruptions of volcano's can cause emission of gasses such as SO_2, CO and CO_2, but also of several heavy metals, such as lead (Burhan & Mukminin, 2020). Forest fires can emit CO and SO_2 as well, but additionally also NO_2, O_3 and PM (Burhan & Mukminin, 2020). Other examples of natural sources are lightning strikes, dust storms, biological decay and plants (Singh & Sharma, 2018).

Traffic

One of the main anthropogenic sources is traffic, which includes both road and non-road traffic (European Environment Agency, 2021). The main mechanism causing air pollution in this category is the combustion of fossil fuels in motor vehicles. This results in the formation of, among others, NO_2 and PM (Iskandar et al., 2012; Kelly & Fussell, 2011). Most PM emissions can be attributed to diesel-powered vehicles (Kelly & Fussell, 2011; Lelieveld et al., 2020). Emissions of NO_x, on the other hand, are just as important. Of all NO_x emissions in Europe in 2019, 46% were due to transport (European Environment Agency, 2021). As a results, in places with a lot of traffic and high NO_2 concentrations, this can cause smog due to formation of O_3 from NO_2 (Kelly & Fussell, 2011).

Agriculture

An anthropogenic source that is more related to rural areas is agriculture. The main pollutants in this category are due to the usage of soil enriching substances containing nitrogen. This includes ammonia (NH_3), ammonium (NH_4^+), nitrogen oxides (NO_x) and nitrous oxide (N_2O) (Bertora et al., 2010;

European Environment Agency, 2021; Olsson et al., 2021). Of these substances, NH_3 can react with oxidised SO_2 and NO_2, thereby extending its time in the atmosphere (Bertora et al., 2010). In addition, NH_3 is also one of the precursors of PM (Bertora et al., 2010; Guerreiro et al., 2014).

Another often emitted compound from agriculture is methane (CH_4), a VOC. This compound originates among others from livestock manure and cultivation of crops, such as rice (Bertora et al., 2010). CH_4, carbon monoxide (CO), and other VOCs that originate from animal manure also contribute to air pollution as they can be precursors of ozone (Bertora et al., 2010). This might explain higher ozone concentrations at rural sites in comparison to urban sites (Guerreiro et al., 2014). Guerreiro et al. (2014) argued, on the other side, that this has more to do with the removal of O_3 in urban areas by NO emissions.

Other substances playing a role in agriculture are persistent organic pollutants (POPs). This group includes many pesticides and fungicides that are used to prevent plagues and diseases (Bertora et al., 2010). In contrast, agriculture emits relatively less carbon dioxide (CO_2). Yet, in case of a land use change where the main source of carbon dioxide, namely trees, is cut down, agriculture can be an important source (Bertora et al., 2010).

Industrial

A source that is present in both rural and urban areas is industry. This source consists of two main sources, namely power plants and factories (European Environment Agency, 2021).

The emission of power plants can differ, depending on their source. Common sources burned to generate energy are coal, gas, oil and biomass (Lelieveld et al., 2020). Compounds released from these energy generating factories are CO_2, PM, SO_2, O_3, NO_x, CH_4, secondary organic aerosols (SOA), black carbon (BC) and primary organic carbon (pOC) (Bertora et al., 2010; Dąbrowiecki et al., 2022; European Environment Agency, 2021; Guarnieri & Balmes, 2014; Olsson et al., 2021).

Factories include both factories that manufacture products and factories that extract resources. Two key emitted compounds of factories are SO_2 and CO_2. The emission of SO_2 is especially high in factories where they work with raw materials such as smelters (Guerreiro et al., 2014). Furthermore, SO_2 contributes to the emission of PM as a precursor (Guerreiro et al., 2014). Another group of pollutants that is often emitted by factories, are toxic metals such as lead, cadmium and mercury (Guerreiro et al., 2014).

Residential

This category refers to pollutants emitted by residential buildings and working places, such as offices. Much has changed in this category in recent decades, as much of the biomass-based domestic cooking and heating has been replaced by gas and sustainable sources (Landrigan, 2017). Yet, emission levels of particularly polycyclic aromatic hydrocarbons (PAHs) and PM are still high (Guerreiro et al., 2014). The European Environment Agency (2021) described in their rapport that in 2019 of all the emitted PM_{10} and $PM_{2.5}$, 40% and 53% was emitted by the residential sector.