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THE AIR POLLUTION IMPACT ON PULMONARY EXACERBATIONS AND RESPIRATORY FUNCTION IN PATIENTS WITH CYSTIC FIBROSIS

Elena Gjinovska-Tasevska[1], Emilija Vlashki[2], Tatjana Jakjovska[1,2], Katerina Boshkovska[1,2], Ivana Arnaudova Daneva[1,2], Filip Doksimovski[1], Hristijan Nestorov[1], Enfale Ismaili[1]
[1]University Clinic for Respiratory Diseases in Children -Kozle in Skopje, North Macedonia,
[2]Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, North Macedonia

Abstract

Pulmonary exacerbations in cystic fibrosis (CF) contribute to the burden of disease, with a negative impact on quality of life, treatment costs, but most significantly affect lung function. Data regarding the impact of environmental factors, especially air pollution, on CF are limited.

This study aimed to assess the impact of air pollutants on pulmonary exacerbations and lung function in CF. The study included 25 patients with CF.

Air quality parameters 5 days before and on the day of hospitalization were provided by measuring stations in cooperation with the State Automatic Monitoring System for Ambient Air Quality. Concentrations of PM2.5 and PM10 above the maximum allowed concentration five days before and on the day of exacerbation in almost all patients were determined, with their significant mutual association (highest OR 16.33, $p<0.001$ on the day of exacerbation for PM2.5 and OR 7.0, $p<0.01$ on the third day before exacerbation for PM10).

A significant difference was found in the patient's lung function during periods with and without air pollution ($p<0.001$), with lower values during the periods with air pollution. Air pollution with PM2.5 and PM10 particles was associated with an increased risk of pulmonary exacerbations and reduced lung function in patients with CF.

Keywords: air pollution, cystic fibrosis, exacerbation, lung's function.

Introduction

Long-term air pollution, assessed in various ways (outdoor measurements or municipal pollution, distance to a major road or traffic flow), increases respiratory symptoms in healthy children and adults [1-9]. Asthma, allergic rhinitis and exacerbations of cystic fibrosis (CF) are the most common respiratory consequences of outdoor air pollution [10-17].

With the increased life expectancy of people with CF, the impact of environmental factors on them is becoming increasingly important [18]. On the other hand, pulmonary exacerbations in patients with CF affect the overall quality of life, treatment costs, but most significantly affect lung function [19].

Air pollution has negative effects on patients with CF, who are at particular risk from air pollution. These findings are among the first to be confirmed by Goss et al. [20] and Sathya et al. [2], who show that higher average levels of PM particles and ozone in the air are associated with more severe episodes of lung infections in patients with CF and that lung function deteriorates in those with higher exposure to fine particles.

In North Macedonia, there are 3,828 deaths annually that can be attributed to exposure to current concentrations of PM2.5 particles, which is 17.7 percent of the total mortality in the country. Air pollution is responsible for 11.6% of infant deaths, meaning that one in nine deaths in children under one year of age is related to pollution. Data on the impact of environmental factors, especially air pollution, on CF are limited [21].

Our aim was to assess the association between air pollution and pulmonary exacerbations in CF, as well as the impact of the same on pulmonary function in patients with CF.

Patients and methods

The study was conducted in 25 patients over 6 years of age who were treated at the Cystic Fibrosis Center within the University Clinic for respiratory diseases in children -Kozle in Skopje. Approval for the conduct of this study was issued by the Ethics Committee for Research on Humans within the Medical Faculty in Skopje.

The patients who were included in this study had been diagnosed with CF and signed informed consent. The diagnosis of CF was based on the presence of a positive sweat test and two known CF mutations. Pregnant patients, patients in the terminal phase of the disease, transplant patients, patients with other diseases and patients with CF who were currently diagnosed with another acute viral cause were excluded from the study.

Acute viral infections are excluded with rapid chromatographic test for viral antigen detection. Pulmonary exacerbation was defined as the onset of intravenous or oral antibiotic use requiring hospitalization, but also with the recent change to have at least two of the six validated modified criteria defined by Fuchs et al. [22], Bilton et al. [23], and Ramsey et al. [24].

All episodes of hospitalization for intravenous and oral antibiotic administration due to clinical deterioration or worsening of FEV1 were tested for the analysis. We used modified Fuchs criteria validated by the European consensus group (EuroCareCF Working Group) to define clinical or pulmonary deterioration [23].

During hospitalization due to pulmonary exacerbation in the months with air pollution, each patient was analyzed for: current microbiological isolates from sputum, pulmonary function with spirometry (FVC, FEV1) and air quality parameters in the period 5 days before pulmonary exacerbation and the day of hospitalization. The data were taken retrogradely after the hospitalization of each patient individually.

In the months without air pollution, each patient was analyzed for identical parameters as in the period with air pollution at a regular check-up or possible hospitalization.

Microbiological isolates from sputum were prepared by the cultural method of inoculating sputum on appropriate nutrient media for the growth of bacteria and fungi as well as by automated detection with VITEK MS.

Additionally, an automated antibiogram was prepared with VITEK2 Compact for resistant bacteria. Pulmonary function tests were used to assess pulmonary function. The same were performed on a DATOSPIR touch spirometer. The values are expressed as a percentage of the expected values for gender, age, body weight and height.

The air quality parameters (PM10, PM2.5, CO, NO2, O3 and SO2) of the patients' home zip code 5 days before hospitalization and on the day of hospitalization by calculating the AQI - Air Quality Index (sum of all measured values from the sensors at one station displaying the pollution on the European AQI scale from 0 to 100) are provided by the measuring stations in the cities in cooperation with the State Automatic Monitoring System for Ambient Air Quality. Namely, air quality monitoring in the Republic of North Macedonia is carried out by the Ministry of Environment and Spatial Planning, which manages the State Automatic Air Quality System, as well as the Institute of Public Health (IPH) with the Public Health Centers (CPH) in Skopje and Veles.

All these data are public and available on the following website https://air.moepp.gov.mk/.

Results

A total of 25 patients (male – 84%; average age 26 ± 0.9 years SD) were analyzed over a period of one year. Pancreatic insufficiency was present in 96% of the patients. According to the cystic fibrosis genotype, 53% were homozygous DelF508/DelF508, 35% heterozygous DelF508/other mutation, and 12% with other CF mutations.

A total of 57 hospitalizations due to pulmonary exacerbation were recorded, which corresponds to the same number of intravenous antibiotic treatments. Of the total number of hospitalizations, 70.2% occurred during the period of increased air pollution. The distribution by month is shown in Figure 1.

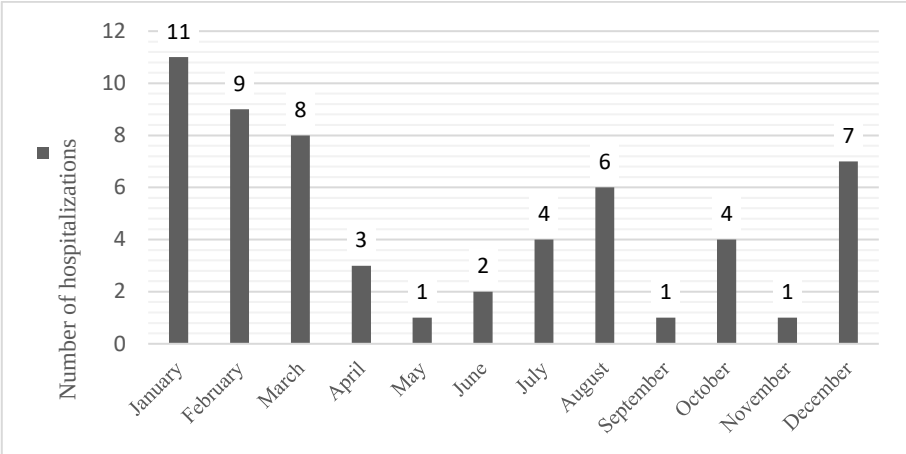

Figure 1. Monthly distribution of hospitalizations.

Of all the air quality parameters analyzed in our study, the largest impact on pulmonary exacerbations had the small, suspended particles PM2.5 and PM10. The remaining parameters (ozone, CO, NO_2 and SO_2) were within the reference values allowed for 24-hour concentrations.

PM2.5 concentrations were increased above the maximum permitted limits (allowed 24-hour concentration: 25 μg/m³) five days before the exacerbation and on the day of the exacerbation in the majority of patients. The highest concentration values were observed on the third day before hospitalization.

Similar results were obtained for PM10 particles (allowed 24-hour concentration: 50 μg/m³). On the day of the pulmonary exacerbation in 32% of patients (8 people) had normal values of concentrations of these particles.

The average 24-hour concentrations of PM2.5 and PM10 are shown in Fig. 2 and Fig. 3.

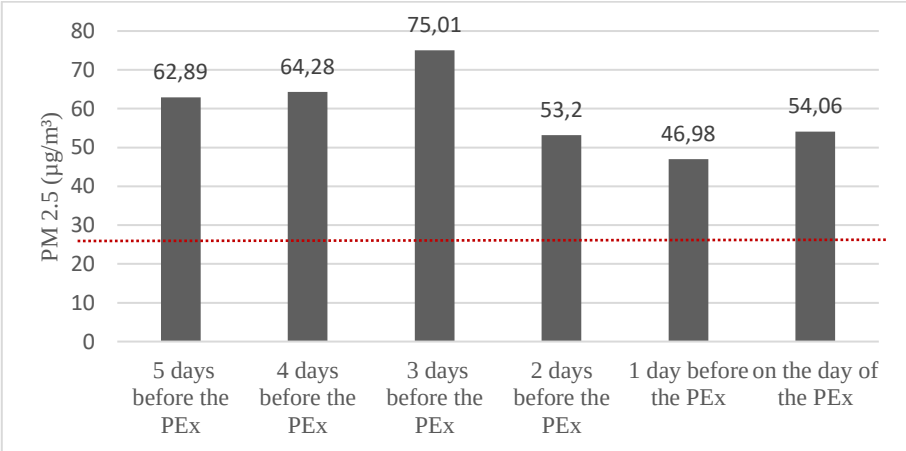

Figure 2. Average 24-hour concentrations of PM2.5, five days before and on the day of pulmonary exacerbation (PEx).

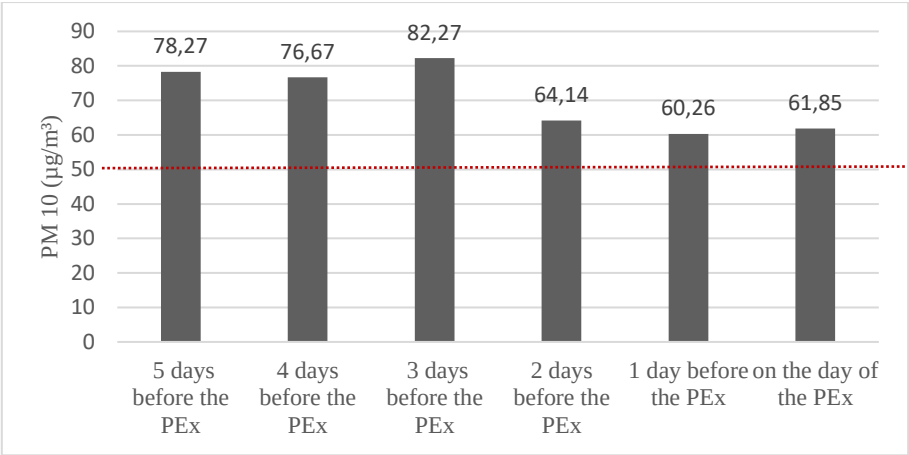

Figure 3. Average 24-hour concentrations of PM10, five days before and on the day of pulmonary exacerbation (PEx).

The values of PM2.5 and PM10 show a strong association with pulmonary exacerbation (PEx). The highest Odds Ratio (OR) for PM2.5 was noted on the day of exacerbation (OR = 16.33), indicating a significantly increased risk of developing PEx at higher concentrations of fine particles. For PM10, the highest OR was 7.0, measured three days before PEx onset, indicating that the effect of larger particles may have a delayed effect.

Table 1 shows the OR values for different time intervals relating to the day of exacerbation.

Table 1. Odds ratio (OR) and p-values for PM2.5 and PM10 by days before/on pulmonary exacerbation (PEx) by number of patients.

	PM2.5				**PM10**			
Day before / on PEx	**High (>25 µg/m³)**	**Normal (≤25 µg/m³)**	**OR**	**p**	**High (>50 µg/m³)**	**Normal (≤50 µg/m³)**	**OR**	**p**
5 days	22	3	6.43	0.01	21	4	5.25	0.02
4 days	22	3	6.43	0.01	21	4	5.25	0.02
3 days	21	4	4.78	0.03	22	3	7	0.01
2 days	21	4	4.78	0.03	21	4	5.25	0.02
1 day	21	4	4.78	0.03	20	5	4.33	0.04
day	24	1	16.33	<0.001	21	4	5,25	0.02

As previously mentioned, the remaining air pollutants on the day of hospitalization were within the maximum permitted concentrations. Thus, for SO2, the mean daily average value was 3.8 µg/m^3 (maximum permitted mean daily limit value is 125 µg/m^3), the mean average value for NO2 was 62.44 µg/m^3 (maximum permitted hourly average concentration is 200 µg/m^3 for one hour).

The alarm threshold for NO_2 is 400 µg/m^3, over three consecutive hours. The maximum daily eight-hour value of the CO concentration is 10 µg/m^3, while our mean value of 1.6 µg/m^3 was far below it. For O3, the maximum allowed daily eight-hour concentration values are 120 µg/m^3, while our mean value was 31.14 µg/m^3.

Fig. 4 graphically shows the dynamics of the association between PM2.5 and PM10 concentrations and the occurrence of pulmonary exacerbation with statistical significance ($p<0.05$).

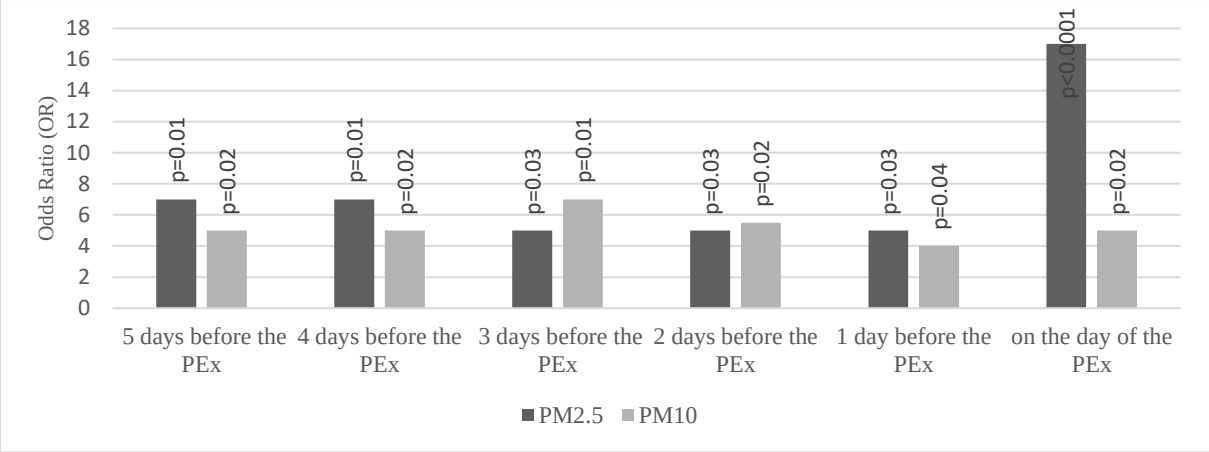

Figure 4. Graphical presentation of the odds ratio (OR) and p-values for PM2.5 and PM10 by days before/on pulmonary exacerbation (PEx).

Although the concentrations of other air pollutants, except for PM2.5 and PM10, were within the permissible limits, the air quality index (AQI) still indicated worrying values. Namely, in the majority of patients, the pulmonary exacerbations were in a period when the AQI ranged from 150 to 200, which according to the standards falls into the category of 'unhealthy air quality' for all categories of the population.

These results indicate that despite the lower levels of some pollutants, the increased concentration of PM2.5 and PM10 particles has a significant impact on the overall air quality and the potential risk to the health of the population.

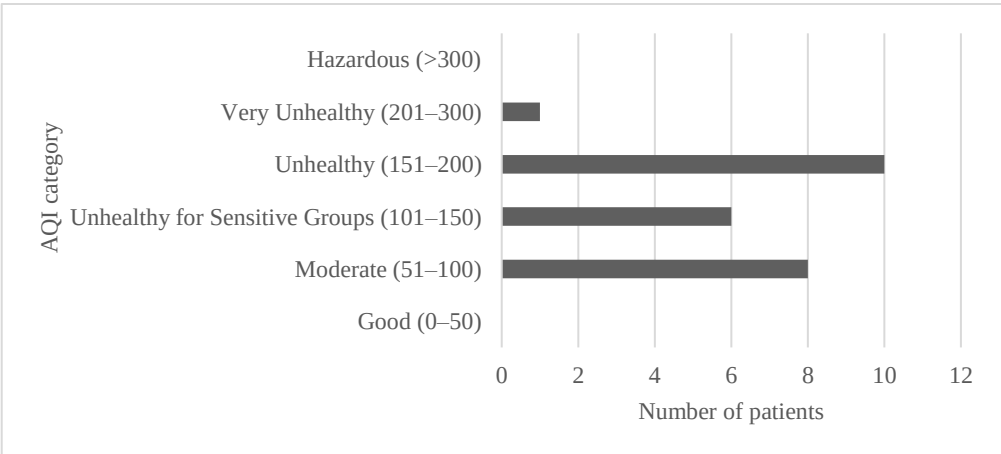

Figure 5. Number of patients by air quality category.

A statistically significant difference was found in the lung function of patients in the periods with and without air pollution. The mean value of FEV_1 in the period without air pollution was 79.23 ± 5.33 SD, while in the period with air pollution it was 69.45 ± 5.37 SD.

The mean value of FVC in the period without air pollution was 89.84 ± 4.38 SD, compared to 78.58 ± 4.35 SD in the period with air pollution. The results show that both FEV1 and FVC are significantly lower in the periods with air pollution, with statistically significant t-values obtained (FEV_1: $t = 6.46$, $p < 0.001$; FVC: $t = 7.39$, $p < 0.001$) (Table 2).

These results indicate a negative impact of air pollution on lung function.

Table 2. Difference in FVC and FEV1 in periods with and without air pollution.

	Differences in pairs				Significance	
	Mean value	Standard deviation	Standard error (SGS)	t-value	p-value (one-way hypothesis)	p-value (two-way hypothesis)
Difference in FEV1 without and with air pollution	9.7792	7.4113	1.5128	6.464	<0.001	<0.001
Difference in FVC without and with air pollution	11.2625	7.4666	1.5241	7.39	<0.001	<0.001

The distribution of pathogenic microorganisms specific for CF in the periods with and without air pollution is shown in Figure 6.

Due to the small total number of patients, and of them an even smaller number of different positive isolates, a statistical analysis of them could not be performed and the data are not sufficient to reliably determine the impact of air pollutants on them.

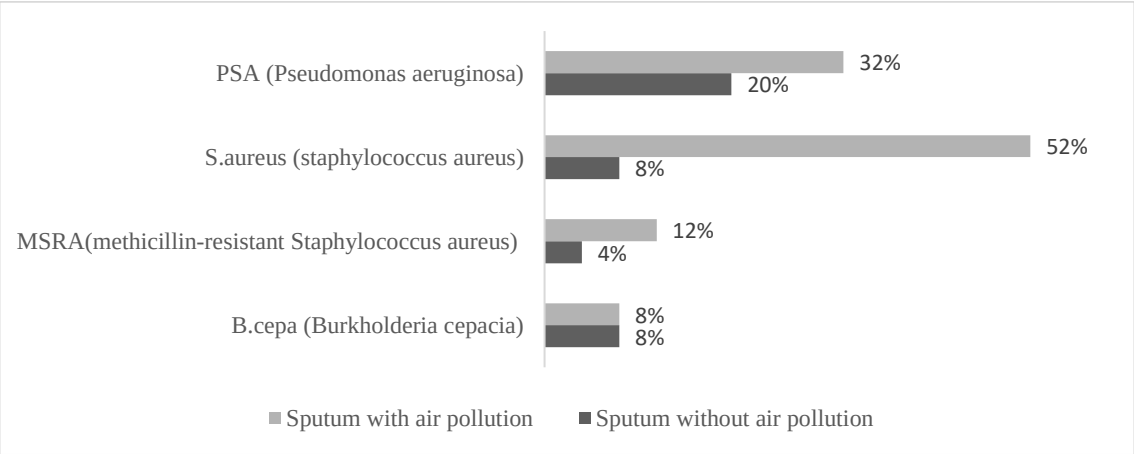

Figure 6. Microbiological distribution of pathogenic bacteria in sputum of patients with CF during periods with and without air pollution.

Discussion

Pulmonary exacerbations in CF contribute to the overall outcome of the disease, as well as the quality of life of people with CF [18, 19]. Air pollutants from the indoor and outdoor environments have a particular impact on them [2, 3].

Air pollution as one of the main culprits of harmful effects from the outdoor environment is the subject of several studies [20, 25].

In our study, the mean value of the 24-hour concentration of PM2.5 and PM10, 5 days before and on the day of pulmonary exacerbation was well above the permissible concentrations according to our norms and those prescribed within Europe, but also by the WHO [18].

High values of small suspended particles had an impact on the number of pulmonary exacerbations requiring antibiotic therapy, as well as on the decline in lung function, but also on the appearance of certain microbial isolates. All this was especially pronounced during the winter months

when air pollution is also increased. Goeminne et al. [17], determined that chronic colonization with Pseudomonas versus non-chronic colonization did not show significant differences in exacerbations caused by air pollution. In this study, the number of exacerbations did not differ between seasons, although a stronger effect of air pollution on exacerbations was observed during the warmer months, unlike our study where the number of pulmonary exacerbations and the negative effects of air pollution were absolutely increased in the colder months.

In summary, the mean value of air pollutants is certainly higher during the winter months in our country and in countries with cold winters that require heating, and hence the source of air pollutants is greater [25].

In regions with intensive use of wood for heating, studies show high concentrations of PM2.5, PM10 and volatile organic compounds (VOC). In many cities around the world, wood heating is a dominant source of pollution and contributes up to 95% of the measured PM concentrations in the winter period. According to the WHO, as many as 28 components in wood combustion emissions have been defined as toxic, of which 14 are carcinogenic [26]. In addition, non-specific particulate matter (PM) originating from wood and coal combustion has recently been classified by the IARC (International Agency for Research on Cancer) as carcinogenic [27].

In the first published study related to air pollution and CF by Goss et al. [20], in 2004 which analyzed 24-hour average exposure to particulate matter (PM2.5 and PM10) and annual average exposure to carbon monoxide, ozone, nitrogen dioxide, and sulfur dioxide, it was concluded that patients with two or more exacerbations lived in areas with slightly elevated concentrations of PM2.5 and PM10 and with normal annual average levels of CO, SO2, or NO2. In contrast, in our study, significantly increased concentrations of PM2.5 and PM10 were associated with two or more exacerbations, but without an effect on the daily average levels of other air pollutants, as in the above-mentioned study.

On the other hand, completely different conclusions were reached in the study by Jassal et al. [28], who guided by the fact that traffic is the main source of small particles and NO2, compared the proximity of residential buildings to highways or major roads as well as the maximum annual 1-hour O3 and annual average concentrations of PM2.5 with exacerbations of CF. No connection was observed with exposure to O3 or PM2.5 with exacerbations in CF.

No connection was observed with the proximity of residential buildings to highways (OR 1.12, 95% CI 0.30-66.53), but a positive connection was observed for the distance to the ‘main road’.

In the study conducted by Psoter et al. [29], the impact of early exposure to PM2.5 on the primary infection with Pseudomonas was proven. Each increase in PM2.5 exposure of 10 $\mu g/m^3$ was associated with a 24% increased risk of acquiring Pseudomonas.

In our study, although there were no patients with primary infection with Pseudomonas aeruginosa, we still found that exposure to air pollution causes an increase in the colonization of pathogenic bacteria in the respiratory tract of patients with CF, especially Staphylococcus aureus, including methicillin-resistant Staphylococcus aureus (MRSA), as well as Pseudomonas aeruginosa.

Although a much higher number of infections with Staphylococcus aureus has been observed during the period of air pollution, due to the small number of patients, this is still an area that needs to be researched. Of course, both pathogenic microorganisms have a negative impact on lung function and increase the risk of pulmonary exacerbation.

According to current knowledge, despite the extended life expectancy of people with CF, pulmonary exacerbations with a decline in lung function continue to be the biggest problem [30]. FEV1 is a key predictor of mortality in CF [31].

Although it is understood that every pulmonary exacerbation is associated with a decline primarily in FEV1[31], it is much more important that Ittner et al. [33], reported that this decline in vital parameters almost never returns to the beginning, hence the need to reduce to a minimum the effects that lead to an increased number of pulmonary exacerbations.

Conclusion

From the data available so far and their analysis in this study, it is concluded that there is an evident impact of air pollution on patients with CF. Small suspended particles such as PM2.5 and PM10 had a particular impact, especially in the colder months. They affect the number of pulmonary exacerbations, decline in respiratory function and probably the microbial isolates in these patients.

References

1. Pierse N. Locally generated particulate pollution and respiratory symptoms in young children. Thorax. 2006; 61(3):216–20.
2. Sathya SA, Ishaan S, Om PK. Air quality and respiratory health in children. Breathe. 2023; 19(2):230-40.
3. Ines R, Monica UL, Carolyn D, Mark N, Mireia G. The Health-Related and Learning performance effects of pollution and other urban-related environmental factors on school-age children and adolescents-A scoping Review of Systematic Reviews. Curr Environ Health Rep. 2024; 11:300-16.
4. Keshuo L, Huanhuan Z, Yacong B, et al. Ambient air pollution and Children's health: An umbrella review. Atmos Pollut Res. 2024; 15:102-8.
5. Hertz-Picciotto I, Baker RJ, Yap PS, et al. Early childhood lower respiratory illness and air pollution. Environ Health Perspect. 2007; 115:1510-8.
6. Jedrychowski WA, Perera FP, Spengler JD, et al. Intrauterine exposure to fine particulate matter as a risk factor for increased susceptibility to acute bronchopulmonary infections in early childhood. Int J Hyg Environ Health. 2013; 216:395-401.
7. Macintyre EA, Gehring U, Molter A. et al. Air pollution and respiratory infections during early childhood: An analysis of 10 European birth cohorts within the escape project. Environ Health Perspect. 2013; 22:22.
8. Peel JL, Tolbert PE, Klein M, et al. Ambient air pollution and respiratory emergency department visits. Epidemiology. 2005; 16:164–74.
9. American Thoracic Society. What Constitutes an Adverse Health Effect of Air Pollution? Am J Respir Crit Care Med. 2000; 161(4):65-73.
10. Gehring U, Wijga AH, Brauer M, et al. Traffic-related Air Pollution and the Development of Asthma and Allergies during the First 8 Years of Life. Am J Respir Crit Care Med. 2010; 181(6):596–603.
11. Vlaski E, Stavric K, Seckova L, Kimovska Hristova M, Isjanovska R. The self-reported density of truck traffic on residential streets and the impact on asthma, hay fever and eczema in young adolescents. Allergol Immunopathol (Madr). 2014; 42(3):224-9.
12. Anderson HR, Butland BK, van Donkelaar A, et al. and the ISAAC Phase One and Phase Three study groups. Satellite-based Estimates of Ambient Air Pollution and Global Variations in Childhood Asthma Prevalence. Environ Health Perspect. 2012; 120(9):1333-9.
13. Brauer M, Hoek G, Smit HA, et al. Air pollution and development of asthma, allergy and infections in a birth cohort. Eur Respir J. 2007; 29(5):879–88.
14. Shima M, Nitta Y, Ando M, Adachi M. Effects of Air Pollution on the Prevalence and Incidence of Asthma in Children. Arch Environ Health. 2002; 57(6):529-35.
15. Hwang BF, Jaakkola JJ, Lee YL, Lin YC, Guo YL. Relation between air pollution and allergic rhinitis in Taiwanese schoolchildren. Respir Res. 2006; 7:23–9.
16. Lee Y-L, Shaw C-K, Su H-J, et al. Climate, traffic-related air pollutants and allergic rhinitis prevalence in middle-school children in Taiwan. Eur Respir J. 2003; 21(6):964–70.
17. Goeminne PC, Kiciński M, Vermeulen F, et al. Impact of Air Pollution on Cystic Fibrosis Pulmonary Exacerbations. Chest. 2013; 143(4):946–54.
18. Brugha R, Edmondson C, Davies JC. Outdoor Air Pollution and Cystic Fibrosis. Paediatr Respir Rev. 2018; 18:80-6.
19. Goldbeck L, Zerrer S, Schmitz TG. Monitoring quality of life in outpatients with cystic fibrosis: feasibility and longitudinal results. J Cyst Fibros. 2007; 6(3):171-8.
20. Goss CH, Newsom SA, Schildcrout JS, Sheppard L, Kaufman JD. Effect of ambient air pollution on pulmonary exacerbations and lung function in cystic fibrosis. Am J Respir Crit Care Med. 2004; 169(7):816-21.
21. Извештај за проценка на влијанието на загадениот воздух со лебдечки честички врз здравјето на луѓето и проценка на оптоварување со болести за 2024 година, Институт за Јавно Здравје на Р.С.Македонија https://www.iph.mk/mk/news/index/1508

22. Fuchs HJ, Borowitz DS, Christiansen DH, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. N Engl J Med. 1994; 331(10):637–42.
23. Bilton D, Canny G, Conway S, et al. Pulmonary exacerbation: Towards a definition for use in clinical trials. Report from the EuroCareCF Working Group on outcome parameters in clinical trials. J Cyst Fibros. 2011; 10:79–81.
24. Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. N Engl J Med. 1999; 340(1):23–30.
25. Wine O, Vargas AO, Campbell SM, Hosseini V, Koch CR, Shahbakhti M. Cold climate impacte on air-polution-related health outcomes: A scoping review. J Environ Res Public Health. 2022; 19(3):1473.
26. Smith KR, Bruce N, Balakrishnan K, et al. Millions Dead: How Do We Know and What Does It Mean? Methods Used in the Comparative Risk Assessment of Household Air Pollution. Annu Rev Public Health. 2014; 35(1):185–206.
27. Loomis D, Grosse Y, Lauby-Secretan B, et al. The carcinogenicity of outdoor air pollution. The Lancet Oncol. (2013); 14(13):1262–63.
28. Jassal MS, Yu AM, Bhatia R, Keens TG, Davidson Ward SL. Effect of residential proximity to major roadways on cystic fibrosis exacerbations. Int J Environ Health Res. 2013; 23(2):119–31.
29. Psoter KJ, De Roos AJ, Mayer JD, Kaufman JD, Wakefield J., Rosenfeld M. Fine Particulate Matter Exposure and Initial Pseudomonas aeruginosa Acquisition in Cystic Fibrosis. Ann Am Thorac Soc. 2015; 12(3):385–91.
30. Britto MT, Kotagal UR, Hornung RW, Atherton HD, Tsevat J, Wilmott RW. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. Chest. 2002; 121(1): 64-72.
31. Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. Am J Epidemiol. 2001;153(4):345-52.
32. Sanders DB, Bittner RC, Rosenfeld M, Redding GJ, Goss CH. Pulmonary exacerbations are associated with subsequent FEV1 decline in both adults and children with cystic fibrosis. Pediatr Pulmonol. 2011; 46(4):393-400.
33. Ittner RC, Rosenfeld M, Hoffman LR, Redding GJ, Goss CH. Failure to recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation. Am J Respir Crit Care Med. 2010; 182(5):627-32.