Review

trd Tuberculosis & Respiratory Diseases

Adverse Effects of Air Pollution on Pulmonary Diseases

https://doi.org/10.4046/trd.2022.0116
ISSN: 1738-3536(Print)/
2005-6184(Online)
Tuberc Respir Dis 2022;85:313-319

Ui Won Ko, M.D. and Sun Young Kyung, M.D., Ph.D.
Department of Allergy, Pulmonology and Critical Care Medicine, Gachon University Gil Medical Center, Incheon, Republic of Korea

Address for correspondence
Sun Young Kyung, M.D., Ph.D.
Department of Allergy, Pulmonology and Critical Care Medicine, Gachon University Gil Medical Center, 21 Namdong-daero 774beon-gil, Namdong-gu, Incheon 21565, Republic of Korea
Phone 82-32-460-2634
Fax 82-32-469-4320
E-mail light@gilhospital.com
Received Aug. 16, 2022
Revised Sep. 8, 2022
Accepted Sep. 13, 2022
Published online Sep. 13, 2022

Abstract

Environmental exposure to air pollution is known to have adverse effects on various organs. Air pollution has greater effects on the pulmonary system as the lungs are directly exposed to contaminants in the air. Here, we review the associations of air pollution with the development, morbidity, and mortality of pulmonary diseases. Short- and long-term exposure to air pollution have been shown to increase mortality risk even at concentrations below the current national guidelines. Ambient air pollution has been shown to be associated with lung cancer. Particularly long-term exposure to particulate matter with a diameter <2.5 μm ($PM_{2.5}$) has been reported to be associated with lung cancer even at low concentrations. In addition, exposure to air pollution has been shown to increase the incidence risk of chronic obstructive pulmonary disease (COPD) and has been correlated with exacerbation and mortality of COPD. Air pollution has also been linked to exacerbation, mortality, and development of asthma. Exposure to nitrogen dioxide (NO_2) has been demonstrated to be related to increased mortality in patients with idiopathic pulmonary fibrosis. Additionally, air pollution increases the incidence of infectious diseases, such as pneumonia, bronchitis, and tuberculosis. Furthermore, emerging evidence supports a link between air pollution and coronavirus disease 2019 transmission, susceptibility, severity and mortality. In conclusion, the stringency of air quality guidelines should be increased and further therapeutic trials are required in patients at high risk of adverse health effects of air pollution.

Keywords: Air Pollution; Chronic Obstructive Pulmonary Disease; Asthma; COVID-19; Idiopathic Pulmonary Fibrosis; Lung Cancer; Mortality

Introduction

Air pollution, contaminated water, soil, food, and occupational exposure to various harmful materials are well-known environmental risk factors with potential adverse effects on human health[1]. These environmental exposures are known to induce a number of cellular and molecular processes, including oxidative stress, inflammation, genetic alterations, mutations, epigenetic alterations, mitochondrial dysfunction, endocrine disruption, and altered intracellular communication[1]. Exposure of lung epithelial cells to particulate matter (PM) consisting of mixtures of transition metals and other secondary substances produced from gaseous pollution, induces the production of reactive oxygen species, resulting in inflammation, cell death, and organ damage[2,3]. Furthermore, somatic mutations and epigenetic alterations, such as DNA methylation, induced by environmental exposures can affect the development of chronic diseases or cancer[4,5]. In the pulmonary system, immune cell interactions, altered lung microbiome, and virus activation are also important pathogenetic processes that result in the increased incidence of infectious lung diseases, such as pneu-

monia and bronchitis, as well as exacerbation of respiratory diseases[1]. In addition, there is evidence that air pollution affects all organs through these processes, including the occurrence and exacerbation of chronic diseases, such as cancer, cardiovascular, cerebrovascular, and metabolic diseases[1].

The World Health Organization (WHO) has estimated that 12.6 million deaths are attributable to environmental factors annually around the world[6]. Among these environmental risks, the burden of disease caused by air pollution is increasing, and PM was estimated to be responsible for 9 million premature deaths, representing to one in six deaths globally every year[7].

The main ambient air pollutants for which there is accumulating evidence of adverse health effects include PM, nitrogen oxides (NOx and NO_2), ozone (O_3), sulfur dioxide (SO_2), and carbon monoxide (CO)[8]. PM is classified according to particle size as $PM_{2.5}$ and PM_{10} with particle diameters of <2.5 μm and <10 μm, respectively[9]. The levels of these pollutants are continuously monitored worldwide as a means of determining air quality in a given area. Indoor air pollution represents household air pollution from multiple sources, such as cooking and heating using solid fuels or burning of biomass[8].

Here, we present a review of recent studies regarding the effects of ambient and indoor air pollution on the development, morbidity, and mortality of pulmonary diseases.

Air Pollution and Mortality

Many previous studies performed around the world have yielded convincing evidence for associations of short- and long-term exposure to air pollution with mortality. In 1992, Dockery et al.[10] reported increases of 16%–17% in daily mortality risk for each 100 μg/m^3 increase in PM, and Pope et al.[11] reported that an increase in 5-day moving average PM_{10} level of 100 μg/m^3 was associated with an estimated increase in daily mortality rate of 16%. A recent systematic evaluation of time-series studies regarding the association of PM_{10} and $PM_{2.5}$ with daily mortality in more than 600 cities around the world indicated that an increase of 10 μg/m^3 in the 2-day moving average of PM_{10} concentration was associated with increases of 0.44% in daily all-cause mortality rate and 0.47% in daily pulmonary mortality rate, with corresponding increases of 0.68% and 0.74% in daily mortality rates for the same change in $PM_{2.5}$ concentration, respectively[12].

A study in six cities in the United States reported that long-term exposure to $PM_{2.5}$ was associated with increases of 1.26-fold in all-cause mortality rate and 1.37-fold in the cardiopulmonary mortality rate for the cities with the highest versus the lowest levels of air pollution[13]. Recently, Di et al.[14] reported increases in annual all-cause mortality rates of 7.3% per increase of 10 μg/m^3 in $PM_{2.5}$ and 1.1% per increase of 10 ppb in O_3. These authors reported that air pollution can have adverse effects at low concentrations, below the current national standards[14]. Similar to this study, exposure to air pollution at concentrations below the WHO guidelines has been shown to affect mortality. A population-based study of Medicare beneficiaries over 65 years old in the southeastern USA suggested that long-term exposure to low levels of NO_2 at concentrations below the guidelines can increase mortality risk by 4.7%[15].

A recent study based on the Effects of Low-level Air Pollution Study in Europe (ELAPSE) cohort, which extended the European Study of Cohorts for Air Pollution Effects (ESCAPE) cohort from six European countries, suggested that the increase in mortality due to long-term $PM_{2.5}$ exposure is most likely due to vanadium[16].

Air Pollution and Lung Cancer

The ESCAPE study evaluated the association between long-term exposure to ambient air pollution and incidence of lung cancer, and showed significant hazard ratios (HRs) for PM_{10} of 1.22 for all lung cancers and 1.51 for adenocarcinoma[17]. Based on these results, the International Agency for Research on Cancer (IARC) has classified PM as group 1 carcinogen to humans[18].

Recently, results from the ELAPSE study about the relations of low-level air pollutants, including $PM_{2.5}$, NO_2, black carbon, and O_3, with the incidence of lung cancer were reported[19-21]. The risk of lung cancer was shown to increase with higher levels of exposure to $PM_{2.5}$, with a HR of 1.13[19]. However, NO_2, black carbon, and O_3 showed no associations with the development of lung cancer[19]. A prospective study using data from the UK Biobank reported significant associations between the incidence of lung cancer and air pollutants, with HRs of 1.63 per increase of 5 μg/m^3 in $PM_{2.5}$, 1.53 per increase of 10 μg/m^3 in PM_{10}, 1.10 per increase of 10 μg/m^3 in NO_2, and 1.13 per increase of 20 μg/m^3 in NOx[20].

Air Pollution and Chronic Obstructive Pulmonary Disease

Although the most important risk factor for the onset of chronic obstructive pulmonary disease (COPD) is smoking, about 30% of patients are never-smokers[22].

Air pollution has been considered another risk factor for the incidence of COPD; urban PM significantly decreases cell viability and increased oxidative stress and autophagy levels on human bronchial epithelial cells[23]. However, there was still insufficient direct epidemiological evidence linking long-term air pollution exposure to the onset of COPD[22].

Many studies have shown positive relations between pollutants and COPD incidence, with long-term exposure to air pollution associated with impairment of lung function[24-28]. However, other studies, such as those using data from the ESCAPE cohort, showed no such associations[29]. A recent study of ELAPSE project data reported the incidence of COPD according to long-term exposure to low concentrations of air pollution[30]. Of the total of 98,058 participants with a mean follow-up period of 16.6 years, 4,928 developed COPD, and the excess risks of COPD occurrence were 17% per increase of 5 $\mu g/m^3$ in $PM_{2.5}$, 11% per increase of 10 $\mu g/m^3$ in NO_2, and 11% per increase of 0.5×10^{-5} m^{-1} in black carbon[30]. In a population-based cohort study performed in Canada, Shin et al.[31] also reported that the risk of COPD increased by 7%, 4%, and 4% per interquartile range (IQR) increase of 3.4 $\mu g/m^3$ in $PM_{2.5}$, NO_2, and O_3, respectively.

In a trial performed in UK, to evaluate individual exposure, to allow precise evaluation of the effect of air pollution on patients with COPD, personal monitoring of exposure to pollutants and their effects in 115 COPD patients showed that higher levels of NO_2, NO, and CO exposure increased exacerbation risk, and exposure to O_3 was related to dyspnea and peak expiratory flow[32].

Furthermore, recent studies have evaluated improvements in respiratory morbidity of COPD after interventions to reduce indoor pollution[33]. In a blinded randomized controlled trial, Hansel et al.[33] reported a significant difference in St. George's Respiratory Questionnaire score between a group using a portable high-efficiency particulate air (HEPA) filter and a control group using a sham filter for 6 months. This was the first environmental intervention study in patients with COPD, and the results suggested that improvement of air quality can improve symptoms in these patients.

Air Pollution and Asthma

$PM_{2.5}$, NO_2, and O_3 are the major pollutants related to airway inflammation and oxidative stress: NO_2 and O_3 produce airway hyperresponsiveness. Through these several responses and pathways, air pollution is associated with exacerbations, mortality, and even the development of asthma[34].

The association air pollution and incidence of asthma has been well known in children that meta-analysis study showed statistically significant associations for black carbon, NO_2, $PM_{2.5}$, and PM_{10} exposures and risk of asthma onset[35]. Furthermore, Garcia et al.[36] reported that decreases in the levels of NO_2 and $PM_{2.5}$ for 10 years were associated with lower asthma incidence among children in United States. Additionally, ELAPSE project showed that long-term exposure to $PM_{2.5}$, NO_2, and black carbon was associated adult-onset asthma[37].

A case-crossover study was performed to assess the association between short-term exposure to air pollution and asthma mortality in China[38]. The study provided that each IQR increase of $PM_{2.5}$, NO_2, and O_3 was associated with asthma mortality, with odds ratios of 1.07, 1.11, and 1.09, respectively.

There was a randomized clinical trial about effect of classroom air filter purifiers on asthma symptoms in students with active asthma[39]. The number of symptom-days with asthma during a 2-week period in the group used HEPA filter purifiers was 1.6 and the mean was 1.8 symptom-days in children with asthma used sham HEPA filter purifiers. However, results showed that use of HEPA filters in the classrooms did not significantly reduce symptom-days with asthma. Further interventional study may need to consider allergen levels, other source of particle exposure, and asthma symptom at baseline.

Air Pollution and Idiopathic Pulmonary Fibrosis

Acute exacerbations and worsening of idiopathic pulmonary fibrosis (IPF) have been shown to be associated with exposure to O_3, NO_2, and PM, but the association between chronic exposure to air pollution and incidence of IPF was not clear.

Consistent with the results of earlier epidemiological studies, a recent study in a population of 1,114 IPF patients in Korea showed a 17% increase in mortality in association with an increase of 10 ppb in NO_2 level estimated based on residential address[40].

The results of a study by Conti et al.[41] suggested a weak association between NO_2 and IPF incidence. Furthermore, pollution factors, such as metal and wood dust, were shown to have meaningful effects on occupational and environmental risks of IPF[42]. Further detailed studies are required to elucidate the associations between pollution and the incidence of IPF.

Air Pollution and Infectious Lung Disease

The risks of infectious lung diseases, such as pneumonia and bronchiolitis, are increased by exposure to air pollution, especially in childhood[43]. The ESCAPE study investigated the associations of air pollutants, such as NO_2, NOx, $PM_{2.5}$, PM_{10}, with pneumonia[43]. The adjusted odds ratios of pneumonia increased significantly for 1.3 per increase of 10 $\mu g/m^3$ in NO_2 and 1.76 per increase of 10 $\mu g/m^3$ in PM_{10}[43]. Children have greater susceptibility to the effects of environmental pollution than adults due to their less developed immune system, small-sized airways, higher respiratory rates, and longer-term exposure to air pollution of the lower respiratory tract. In a time-series study of ambient PM pollution and adult hospital admissions for pneumonia in China, short-term increases of 10 $\mu g/m^3$ in 3-day moving average levels of $PM_{2.5}$ and PM_{10} were shown to be associated with 0.31% and 0.19% increases in hospital admissions due to pneumonia, respectively[44].

A recent study showed associations between indoor air pollution and susceptibility to tuberculosis infection[45]. Briefly, higher levels of indoor air pollution exposure were shown to increase the odds ratio of latent tuberculosis infection in a cohort of 107 children living with 71 patients with active tuberculosis[45]. Based on these results, further studies regarding the associations of pollution with transmission risk of transmittable diseases, such as tuberculosis, and evaluation of the underlying mechanisms are required.

Both long-term and short-term air pollution may play an important role in the airborne spreading of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and may enhance the incidence of coronavirus disease 2019 (COVID-19). Recently, many studies have reported the influence of $PM_{2.5}$ and PM_{10} on SARS-CoV-2 transmission[46-51]. PM could aggravate neurological symptoms of SARS-CoV-2 and exacerbate respiratory and cardiovascular injuries of COVID-19[52-54]. Moreover, there was a report that air pollution is an important cofactor increasing the risk of mortality from COVID-19[55]. Some studies proposed that PM operates as a virus carrier, promoting its transport through the air[56,57].

However, most studies showing an association between air pollution and COVID-19 infection did not consider potential confounding factors in the correlation analysis. Therefore, more rigorous studies considering several additional confounding factors, such as individual age, population density, and pre-existing comorbidities, should be conducted to determine the impact of air pollution on COVID-19 infection.

Conclusion

Recent large-scale cohort studies have confirmed the correlations of long-term exposure to air pollution with the incidence and clinical exacerbation of respiratory diseases. New findings have shown that exposure to pollution at levels below the WHO guidelines can have adverse health effects, suggesting the necessity of revising the guidelines for air quality.

More precise exposure evaluation, such as individual monitoring, is required to clarify the underlying mechanisms and develop suitable interventions to reduce the adverse health effects of air pollution. Recent studies involving precise monitoring of air pollutant exposure levels in patients with COPD reported that interventions to improve indoor air quality can improve COPD symptoms. Thus, such precise evaluation of exposure and trials to improve air quality are meaningful for patients with chronic pulmonary diseases who are at increased vulnerability to the adverse effects of air pollution.

Recent studies have provided evidence supporting the association between PM and lung cancer incidence risk. From observations showing vulnerability to respiratory infection, it should be considered that infants, children, and people with weakened immune systems are vulnerable to the adverse effects of air pollution.

Authors' Contributions

Conceptualization: Kyung SY. Methodology: Kyung SY. Investigation: Kyung SY. Writing - original draft preparation: Ko UW. Writing - review and editing: Kyung SY. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Funding

No funding to declare.

References

1. Peters A, Nawrot TS, Baccarelli AA. Hallmarks of environmental insults. Cell 2021;184:1455-68.
2. Gonzalez-Flecha B. Oxidant mechanisms in response to ambient air particles. Mol Aspects Med 2004;25:169-82.
3. Mudway IS, Kelly FJ, Holgate ST. Oxidative stress in air pollution research. Free Radic Biol Med 2020;151:2-6.

4. Nwanaji-Enwerem JC, Colicino E, Trevisi L, Kloog I, Just AC, Shen J, et al. Long-term ambient particle exposures and blood DNA methylation age: findings from the VA normative aging study. Environ Epigenet 2016;2:dvw006.
5. Ijomone OM, Ijomone OK, Iroegbu JD, Ifenatuoha CW, Olung NF, Aschner M. Epigenetic influence of environmentally neurotoxic metals. Neurotoxicology 2020;81:51-65.
6. Pruss-Ustun A, Wolf J, Corvalan C, Bos R, Neira M. Preventing disease through healthy environments: a global assessment of the burden of disease from environmental risks. 2nd ed. Geneva: World Health Organization; 2016.
7. Fuller R, Landrigan PJ, Balakrishnan K, Bathan G, Bose-O'Reilly S, Brauer M, et al. Pollution and health: a progress update. Lancet Planet Health 2022;6:e535-47.
8. Rojas-Rueda D, Morales-Zamora E, Alsufyani WA, Herbst CH, AlBalawi SM, Alsukait R, et al. Environmental risk factors and health: an umbrella review of meta-analyses. Int J Environ Res Public Health 2021;18:704.
9. World Health Organization. WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide. Global update 2005. Geneva: World Health Organization; 2006.
10. Dockery DW, Schwartz J, Spengler JD. Air pollution and daily mortality: associations with particulates and acid aerosols. Environ Res 1992;59:362-73.
11. Pope CA 3rd, Schwartz J, Ransom MR. Daily mortality and PM10 pollution in Utah Valley. Arch Environ Health 1992;47:211-7.
12. Liu C, Chen R, Sera F, Vicedo-Cabrera AM, Guo Y, Tong S, et al. Ambient particulate air pollution and daily mortality in 652 cities. N Engl J Med 2019;381:705-15.
13. Dockery DW, Pope CA 3rd, Xu X, Spengler JD, Ware JH, Fay ME, et al. An association between air pollution and mortality in six U.S. cities. N Engl J Med 1993;329:1753-9.
14. Di Q, Wang Y, Zanobetti A, Wang Y, Koutrakis P, Choirat C, et al. Air pollution and mortality in the medicare population. N Engl J Med 2017;376:2513-22.
15. Qian Y, Li H, Rosenberg A, Li Q, Sarnat J, Papatheodorou S, et al. Long-term exposure to low-level NO2 and mortality among the elderly population in the southeastern United States. Environ Health Perspect 2021;129:127009.
16. Chen J, Rodopoulou S, de Hoogh K, Strak M, Andersen ZJ, Atkinson R, et al. Long-term exposure to fine particle elemental components and natural and cause-specific mortality: a pooled analysis of eight European cohorts within the ELAPSE project. Environ Health Perspect 2021;129:47009.
17. Raaschou-Nielsen O, Andersen ZJ, Beelen R, Samoli E, Stafoggia M, Weinmayr G, et al. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). Lancet Oncol 2013;14:813-22.
18. Loomis D, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, et al. The carcinogenicity of outdoor air pollution. Lancet Oncol 2013;14:1262-3.
19. Hvidtfeldt UA, Severi G, Andersen ZJ, Atkinson R, Bauwelinck M, Bellander T, et al. Long-term low-level ambient air pollution exposure and risk of lung cancer: a pooled analysis of 7 European cohorts. Environ Int 2021;146:106249.
20. Huang Y, Zhu M, Ji M, Fan J, Xie J, Wei X, et al. Air pollution, genetic factors, and the risk of lung cancer: a prospective study in the UK biobank. Am J Respir Crit Care Med 2021;204:817-25.
21. Ciabattini M, Rizzello E, Lucaroni F, Palombi L, Boffetta P. Systematic review and meta-analysis of recent high-quality studies on exposure to particulate matter and risk of lung cancer. Environ Res 2021;196:110440.
22. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease [Internet]. Fontana: Global Initiative for Chronic Obstructive Lung Disease; 2022 [cited 2022 Aug 14]. Available from: https://goldcopd.org/2022-gold-reports-2/#.
23. Hur J, Rhee CK, Jo YS. Effects of antioxidant on oxidative stress and autophagy in bronchial epithelial cells exposed to particulate matter and cigarette smoke extract. Tuberc Respir Dis 2022;85:237-48.
24. Ackermann-Liebrich U, Leuenberger P, Schwartz J, Schindler C, Monn C, Bolognini G, et al. Lung function and long term exposure to air pollutants in Switzerland. Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) Team. Am J Respir Crit Care Med 1997;155:122-9.
25. Wang M, Aaron CP, Madrigano J, Hoffman EA, Angelini E, Yang J, et al. Association between long-term exposure to ambient air pollution and change in quantitatively assessed emphysema and lung function. JAMA 2019;322:546-56.
26. Niu Y, Yang T, Gu X, Chen R, Meng X, Xu J, et al. Long-term ozone exposure and small airway dysfunction: the China Pulmonary Health (CPH) study. Am J Respir Crit Care Med 2022;205:450-8.
27. Holm SM, Balmes JR. Systematic review of ozone effects on human lung function, 2013 through 2020. Chest 2022;161:190-201.
28. Doiron D, de Hoogh K, Probst-Hensch N, Fortier I, Cai Y, De Matteis S, et al. Air pollution, lung function and COPD: results from the population-based UK Biobank study. Eur Respir J 2019;54:1802140.
29. Schikowski T, Adam M, Marcon A, Cai Y, Vierkotter A,

Carsin AE, et al. Association of ambient air pollution with the prevalence and incidence of COPD. Eur Respir J 2014;44:614-26.
30. Liu S, Jorgensen JT, Ljungman P, Pershagen G, Bellander T, Leander K, et al. Long-term exposure to low-level air pollution and incidence of chronic obstructive pulmonary disease: the ELAPSE project. Environ Int 2021;146:106267.
31. Shin S, Bai L, Burnett RT, Kwong JC, Hystad P, van Donkelaar A, et al. Air pollution as a risk factor for incident chronic obstructive pulmonary disease and asthma: a 15-year population-based cohort study. Am J Respir Crit Care Med 2021;203:1138-48.
32. Evangelopoulos D, Chatzidiakou L, Walton H, Katsouyanni K, Kelly FJ, Quint JK, et al. Personal exposure to air pollution and respiratory health of COPD patients in London. Eur Respir J 2021;58:2003432.
33. Hansel NN, Putcha N, Woo H, Peng R, Diette GB, Fawzy A, et al. Randomized clinical trial of air cleaners to improve indoor air quality and chronic obstructive pulmonary disease health: results of the CLEAN AIR study. Am J Respir Crit Care Med 2022;205:421-30.
34. Chatkin J, Correa L, Santos U. External environmental pollution as a risk factor for asthma. Clin Rev Allergy Immunol 2022;62:72-89.
35. Khreis H, Kelly C, Tate J, Parslow R, Lucas K, Nieuwenhuijsen M. Exposure to traffic-related air pollution and risk of development of childhood asthma: a systematic review and meta-analysis. Environ Int 2017;100:1-31.
36. Garcia E, Berhane KT, Islam T, McConnell R, Urman R, Chen Z, et al. Association of changes in air quality with incident asthma in children in California, 1993-2014. JAMA 2019;321:1906-15.
37. Liu S, Jorgensen JT, Ljungman P, Pershagen G, Bellander T, Leander K, et al. Long-term exposure to low-level air pollution and incidence of asthma: the ELAPSE project. Eur Respir J 2021;57:2003099.
38. Liu Y, Pan J, Zhang H, Shi C, Li G, Peng Z, et al. Short-term exposure to ambient air pollution and asthma mortality. Am J Respir Crit Care Med 2019;200:24-32.
39. Phipatanakul W, Koutrakis P, Coull BA, Petty CR, Gaffin JM, Sheehan WJ, et al. Effect of school integrated pest management or classroom air filter purifiers on asthma symptoms in students with active asthma: a randomized clinical trial. JAMA 2021;326:839-50.
40. Yoon HY, Kim SY, Kim OJ, Song JW. Nitrogen dioxide increases the risk of mortality in idiopathic pulmonary fibrosis. Eur Respir J 2021;57:2001877.
41. Conti S, Harari S, Caminati A, Zanobetti A, Schwartz JD, Bertazzi PA, et al. The association between air pollution and the incidence of idiopathic pulmonary fibrosis in Northern Italy. Eur Respir J 2018;51:1700397.
42. Park Y, Ahn C, Kim TH. Occupational and environmental risk factors of idiopathic pulmonary fibrosis: a systematic review and meta-analyses. Sci Rep 2021;11:4318.
43. MacIntyre EA, Gehring U, Molter A, Fuertes E, Klumper C, Kramer U, et al. Air pollution and respiratory infections during early childhood: an analysis of 10 European birth cohorts within the ESCAPE Project. Environ Health Perspect 2014;122:107-13.
44. Tian Y, Liu H, Wu Y, Si Y, Li M, Wu Y, et al. Ambient particulate matter pollution and adult hospital admissions for pneumonia in urban China: a national time series analysis for 2014 through 2017. PLoS Med 2019;16:e1003010.
45. Blount RJ, Phan H, Trinh T, Dang H, Merrifield C, Zavala M, et al. Indoor air pollution and susceptibility to tuberculosis infection in urban Vietnamese children. Am J Respir Crit Care Med 2021;204:1211-21.
46. Comunian S, Dongo D, Milani C, Palestini P. Air pollution and COVID-19: the role of particulate matter in the spread and increase of COVID-19's morbidity and mortality. Int J Environ Res Public Health 2020;17:4487.
47. Setti L, Passarini F, De Gennaro G, Barbieri P, Licen S, Perrone MG, et al. Potential role of particulate matter in the spreading of COVID-19 in Northern Italy: first observational study based on initial epidemic diffusion. BMJ Open 2020;10:e039338.
48. Tung NT, Cheng PC, Chi KH, Hsiao TC, Jones T, BeruBe K, et al. Particulate matter and SARS-CoV-2: a possible model of COVID-19 transmission. Sci Total Environ 2021;750:141532.
49. Kayalar O, Ari A, Babuccu G, Konyalilar N, Dogan O, Can F, et al. Existence of SARS-CoV-2 RNA on ambient particulate matter samples: a nationwide study in Turkey. Sci Total Environ 2021;789:147976.
50. Fang F, Mu L, Zhu Y, Rao J, Heymann J, Zhang ZF. Long-term exposure to PM2.5, facemask mandates, stay home orders and COVID-19 incidence in the United States. Int J Environ Res Public Health 2021;18:6274.
51. Nor NS, Yip CW, Ibrahim N, Jaafar MH, Rashid ZZ, Mustafa N, et al. Particulate matter (PM2.5) as a potential SARS-CoV-2 carrier. Sci Rep 2021;11:2508.
52. Borisova T, Komisarenko S. Air pollution particulate matter as a potential carrier of SARS-CoV-2 to the nervous system and/or neurological symptom enhancer: arguments in favor. Environ Sci Pollut Res Int 2021;28:40371-7.
53. Espejo W, Celis JE, Chiang G, Bahamonde P. Environment and COVID-19: pollutants, impacts, dissemination, management and recommendations for facing future epidemic threats. Sci Total Environ 2020;747:141314.
54. Tanwar V, Adelstein JM, Wold LE. Double trouble: combined cardiovascular effects of particulate matter exposure and coronavirus disease 2019. Cardiovasc Res

2021;117:85-95.
55. Pozzer A, Dominici F, Haines A, Witt C, Munzel T, Lelieveld J. Regional and global contributions of air pollution to risk of death from COVID-19. Cardiovasc Res 2020;116:2247-53.
56. Maleki M, Anvari E, Hopke PK, Noorimotlagh Z, Mirzaee SA. An updated systematic review on the association between atmospheric particulate matter pollution and prevalence of SARS-CoV-2. Environ Res 2021;195:110898.
57. Senatore V, Zarra T, Buonerba A, Choo KH, Hasan SW, Korshin G, et al. Indoor versus outdoor transmission of SARS-COV-2: environmental factors in virus spread and underestimated sources of risk. EuroMediterr J Environ Integr 2021;6:30.