JKMS

Original Article
Preventive & Social Medicine

Check for updates

Effects of Air Pollution on Chemosensory Dysfunction in COVID-19 Patients

Young-Sook Choi (ID),[1] Byeong-Su Jeong (ID),[2] Yeon-Kyeng Lee (ID),[3] and Yong-Dae Kim (ID) [4,5]

[1]Compensation & Support Center for COVID-19 Vaccine Injury, Korea Disease Control and Prevention Agency, Cheongju, Korea
[2]Digital Health Devices Division, National Institute of Food and Drug Safety Evaluation, Ministry of Food and Drug Safety, Cheongju, Korea
[3]Division of Healthcare Associated Infection Control, Bureau of Healthcare Safety and Immunization, Korea Disease Control and Prevention Agency, Cheongju, Korea
[4]Department of Preventive Medicine, College of Medicine, Chungbuk National University, Cheongju, Korea
[5]Chungbuk Regional Cancer Center, Chungbuk National University Hospital, Cheongju, Korea

OPEN ACCESS

Address for Correspondence:
Yong-Dae Kim, PhD
Department of Preventive Medicine, College of Medicine, Chungbuk National University, 1 Chungdae-ro, Seowon-gu, Cheongju 28644, Republic of Korea.
Email: ydkim@cbu.ac.kr

Yeon-Kyeng Lee, PhD
Division of Healthcare Associated Infection Control, Bureau of Healthcare Safety and Immunization, Korea Disease Control and Prevention Agency, 187 Osongsaengmyeong 2-ro, Osong-eup, Heungdeok-gu, Cheongju 28159, Korea.
Email: yeonkyenglee@cdc.go.kr

ORCID iDs
Young-Sook Choi (ID)
https://orcid.org/0000-0002-0110-7315
Byeong-Su Jeong (ID)
https://orcid.org/0000-0003-2387-4635

ABSTRACT

Background: In some patients, coronavirus disease 2019 (COVID-19) is accompanied by loss of smell and taste, and this has been reportedly associated with exposure to air pollutants. This study investigated the relationship between the occurrence of chemosensory dysfunction in COVID-19 patients and air pollutant concentrations in Korea.
Methods: Information on the clinical symptom of chemosensory dysfunction, the date of diagnosis, residential area, age, and sex of 60,194 confirmed COVID-19 cases reported to the Korea Disease Control and Prevention Agency from January 20 to December 31, 2020 was collected. In addition, the daily average concentration of air pollutants for a week in the patients' residential area was collected from the Ministry of Environment based on the date of diagnosis of COVID-19. A binomial logistic regression model, using age and gender, standardized smoking rate, number of outpatient visits, 24-hour mean temperature and relative humidity at the regional level as covariates, was used to determine the effect of air pollution on chemosensory dysfunction.
Results: Symptoms of chemosensory dysfunction were most frequent among patients in their 20s and 30s, and occurred more frequently in large cities. The logistic analysis showed that the concentration of particulate matter 10 (PM_{10}) and 2.5 ($PM_{2.5}$) up to 2 days before the diagnosis of COVID-19 and the concentration of sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and ozone (O_3) at least 7 days before the diagnosis of COVID-19 affected the development of chemosensory dysfunction. In the logistic regression model adjusted for age, sex, standardized smoking rate, number of outpatient visits, and daily average temperature and relative humidity, it was found that an increase in the interquartile range of PM_{10}, $PM_{2.5}$, SO_2, NO_2, and CO on the day of diagnosis increased the incidence of chemosensory dysfunction 1.10, 1.10, 1.17, 1.31, and 1.19-fold, respectively. In contrast, the O_3 concentration had a negative association with chemosensory dysfunction.
Conclusion: High concentrations of air pollutants such as PM_{10}, $PM_{2.5}$, SO_2, NO_2, and CO on the day of diagnosis increased the risk of developing chemosensory dysfunction from COVID-19 infection. This result underscores the need to actively prevent exposure to air pollution and prevent COVID-19 infection. In addition, policies that regulate activities and

Yeon-Kyeng Lee (ID)
https://orcid.org/0000-0002-0828-455X
Yong-Dae Kim (ID)
https://orcid.org/0000-0003-4671-8045

products that create high amounts of harmful environmental wastes may help in promoting better health for all during COVID-19 pandemic.

Keywords: COVID-19; Chemosensory Dysfunction; Anosmia; Dysgeusia; Air Pollutant; Korean

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is thought to have originated as a parasitic virus in bats, which has evolved to be able to replicate and spread in human cells.[1] It is known to use angiotensin-converting enzyme 2 (ACE2) receptor, transmembrane protease serine subtype 2 (TMPRSS2), and Furin proteins as pathways to enter human cells. When the S2 domain of the SARS-CoV-2 spike binds to the ACE2 receptor of a human cell, TMPRSS2 cuts the S2 domain, and the S1 domain of the virus binds to Furin protein to allow entry to human cells. Currently, the binding ability and susceptibility to infection with SARS-CoV-2 depends on the level of expression of the ACE2 receptor.[2,3] In addition, the expression of ACE2 receptor is known to increase with exposure to air pollutants.[4,5]

Chemosensory dysfunction has been reported as a characteristic clinical symptom of coronavirus disease 2019 (COVID-19) confirmed patients. These symptoms include anosmia, hyposmia, ageusia, and hypogeusia.[6,7] The mechanism of the olfactory dysfunction caused by COVID-19 infection is not clearly known. One of the most promising hypotheses is a direct inflammation followed by the cytokine storm caused by SARS-CoV-2 infection of ACE2- and TMPRSS2-rich sustentacular cells in small upper nasal non-neuronal cells on olfactory epithelium.[2] Gustatory dysfunction is similar to the mechanism of olfactory dysfunction, in which SARS-CoV-2 mainly penetrates the oral epithelium, taste buds, and salivary gland cells and shows high expression of ACE2, TMPRSS2, and Furin, causing inflammation.[8,9] Since SARS-CoV-2 is mostly introduced into the body through the upper respiratory tract, chemosensory dysfunction caused by upper nasal infections mainly occur in the early stages of infection.

According to the previous results the expression of ACE2 and TMPRSS2 receptors, which are pathways for human infection of SARS-CoV-2 and the starting point of chemosensory abnormalities, are increased by exposure to air pollutants such as particulate matter (PM), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2).[10,11] These facts lead to the hypothesis that chemosensory dysfunction in COVID-19 may be exacerbated through a neuroinflammatory mechanism promoted by environmental pollutant exposure.

Most of the symptoms of COVID-19 disappear by the time the patients come out of quarantine, but chemosensory symptoms such as loss of smell may persist for up to 1.5–6 months.[12] In addition, chemosensory dysfunction can lead to loss of appetite and depression, thereby lowering the patient's quality of life,[13] and it can even lead to life-threatening situations during disasters such as fire or chemical exposure, which require recognition of danger by smell. In particular, since these symptoms are known to occur most frequently among young people with a relatively long life expectancy, measures for prevention and management of these symptoms are essential.[14,15]

This study aimed to evaluate the relationship between short-term exposure to air pollutants and chemosensory dysfunction in COVID-19-confirmed patients.

METHODS

A total of 61,769 COVID-19-confirmed cases were reported through the Korea Disease Control and Prevention Agency from January 20, 2020 to December 31, 2020. Of these, 60,194 cases with residence information were enrolled in this study. Information including the date of diagnosis, residential address (Cities/Gun/Gu units, 227 regions in total), sex, age, and signs of anosmia or dysgeusia were collected from the data of the reported COVID-19 patients. Data on ambient air pollution were provided by the Korea Environment Corporation (https://www.airkorea.or.kr/web/last_amb_hour_data?pMENU_NO=123). We collected the 24-hour mean levels of $PM_{2.5}$, PM_{10}, ozone (O_3), carbon monoxide (CO), NO_2, and SO_2 for each area (511 measuring station). For regions with two or more measuring stations, the arithmetic mean value of the data from all measuring stations was used. Data from 7 days before the diagnosis of COVID-19 to the date of diagnosis were matched with air pollution data of the patient's residence (Gu unit) with the symptom data of the patients. Meteorological data such as 24-hour mean temperature and relative humidity was collected from the Korea Meteorological Administration (https://data.kma.go.kr/data/grnd/selectAsosRltmList.do?pgmNo=36). In regions without a measuring station (77 Gu's), the data of the geographically closest measuring station were used. Regional age-standardized smoking rate and the number of outpatients visits were collected from the Korea Centers for Disease Control and Prevention (https://chs.kdca.go.kr/chs/stats/statsMain.do).

We performed χ^2 test and Student's t-test to evaluate group differences in demographic characteristics. Adjusted odds ratios (ORs) were estimated with 95% confidence intervals (CIs) for the risks associated with as increase in the interquartile rage (IQR) of each air pollutant using binomial logistic regressions for the presence or absence of chemosensory dysfunction in patients with confirmed COVID-19. Due to the lack of individual data, regional average data were used for smoking history and medication usage rates. Therefore, the logistic regression model used age, gender, standardized smoking rate, the number of outpatient visits, 24-hour mean temperature and relative humidity at the regional level as covariates. To examine the short-term effects of air pollution, a lag time of 0 to 7 days from the diagnosis date was evaluated. For statistical analysis, the R-based Rex program (Rex-Pro v3.6.0; Rexsoft, Seoul, Korea) was used, and $P < 0.05$ was used as the criterion for significance.

Ethics statement
This study was approved by the Institutional Review Board (IRB) of the Korea Disease Control and Prevention Agency and the requirement for informed consent was waived (IRB No. 2022-01-04-PE-A).

RESULTS

Although the first confirmed case of COVID-19 was reported in Korea on January 20, 2020, the first occurrence of chemosensory dysfunction was reported on February 29, 2020. At the beginning of the COVID-19 epidemic, the incidence rate of chemosensory dysfunction was relatively low, but an increasing trend was observed from the end of July.

Of the 60,194 confirmed cases of COVID-19 reported from January to December 2020, a total of 1,917 (3.2%) experienced chemosensory dysfunction. Among these, 1,453 (2.4%) were confirmed as showing symptoms of olfactory dysfunction (anosmia or hyposmia), 1,172

(1.9%) were confirmed as showing gustatory dysfunction (ageusia or hypogeusia), and 721 (1.2%) included both smell and taste disorders.

The patients with chemosensory dysfunction included 895 (46.7%) males and 1,022 females (53.3%), and no statistically significant sex-related difference was observed (P = 0.250). The mean age of the patients showing chemosensory dysfunction was 37.98 ± 16.24 years, which was significantly lower than that in the group without chemosensory dysfunction (46.76 ± 20.62 years, $P < 0.001$). When the rate of chemosensory dysfunction was analyzed by stratifying patients into age groups with an interval of 10 years, the proportion of symptomatic patients was 6.5% in the patients aged 20–29 years, followed by 5.7% in those aged 30–39 years and 3.9% in those aged 10–19 years. The frequency of chemosensory dysfunction also showed a significant difference according to the place of residence of patients ($P < 0.001$). In Seoul, 5.0% (956 cases) of all confirmed patients showed chemosensory dysfunction, the highest, followed by Gyeonggi-do and Incheon. In Daegu, where many cases occurred in the early stages of the COVID-19 epidemic, the rate of chemosensory dysfunction was relatively low at 0.5% (**Table 1**).

Table 1. Demographic characteristics of study subjects

Characteristics	Chemosensory dysfunction		Total	P values[a]
	Present	Absent		
Sex				0.250
Male	895 (3.1)	28,002 (96.9)	28,897 (100)	
Female	1,022 (3.3)	30,275 (96.7)	31,297 (100)	
Age, yr	38.0 ± 16.2	46.7 ± 20.6	46.5 ± 20.6	< 0.001
Age group, yr				< 0.001
0–9	4 (0.2)	2,109 (99.8)	2,113 (100)	
10–19	145 (3.9)	3,618 (96.1)	3,763 (100)	
20–29	612 (6.5)	8,822 (93.5)	9,434 (100)	
30–39	424 (5.7)	7,020 (94.3)	7,444 (100)	
40–49	251 (3.0)	8,198 (97.0)	8,449 (100)	
50–59	229 (2.0)	11,159 (98.0)	11,388 (100)	
60–69	160 (1.6)	9,545 (98.4)	9,705 (100)	
70–79	75 (1.6)	4,760 (98.4)	4,835 (100)	
80–89	14 (0.6)	2,476 (99.4)	2,490 (100)	
90–99	3 (0.5)	549 (99.5)	552 (100)	
> 100	0 (0.0)	21 (100)	21 (100)	
Residence				< 0.001
Seoul	956 (5.0)	17,991 (95.0)	18,947 (100)	
Busan	52 (2.6)	1,924 (97.4)	1,976 (100)	
Daegu	42 (0.5)	7,899 (99.5)	7,941 (100)	
Incheon	103 (3.3)	2,993 (96.74)	3,096 (100)	
Gwangju	25 (2.2)	1,092 (97.8)	1,117 (100)	
Daejeon	21 (2.4)	855 (97.6)	876 (100)	
Ulsan	7 (1.0)	707 (99.0)	714 (100)	
Sejong	4 (2.5)	159 (97.5)	163 (100)	
Gyeonggi-do	535 (3.5)	14,945 (96.5)	15,480 (100)	
Gangwon-do	22 (1.8)	1,232 (98.2)	1,254 (100)	
Chungcheongbuk-do	20 (1.7)	1,175 (98.3)	1,195 (100)	
Chungcheongnam-do	30 (1.8)	1,657 (98.2)	1,687 (100)	
Jeollabuk-do	27 (3.1)	836 (96.9)	863 (100)	
Jeollanam-do	9 (1.5)	603 (98.5)	612 (100)	
Gyeongsangbuk-do	27 (1.1)	2,436 (98.9)	2,463 (100)	
Gyeongsangnam-do	23 (1.6)	1,376 (98.4)	1,399 (100)	
Jeju-do	14 (3.4)	397 (96.6)	411 (100)	

Values are presented as number (%) or mean ± standard deviation.
[a]Chi-square test or Student's t-test.

Table 2. Descriptive statistics on environmental variables during the study period

Variables	Min, Max	Quartile 1	Quartile 2	Quartile 3
Air pollutants				
PM_{10}, µg/m³	0.0, 146.6	24.2	32.5	46.6
$PM_{2.5}$, µg/m³	0.0, 92.7	12.2	18.5	28.5
SO_2, ppb	0.0, 18.2	2.7	3.3	3.9
NO_2, ppb	0.0, 72.8	13.4	21.2	31.0
CO, ppm	0.0, 1.3	0.4	0.5	0.6
O_3, ppb	0.0, 93.2	13.5	19.8	27.0
Meteorological data				
Temperature, °C	−14.2, 31.7	1.2	5.8	13.6
Humidity, %	0.0, 100.0	53.0	65.2	77.9

PM_{10} = fine particulate matter with an aerodynamic diameter of < 10 µm, $PM_{2.5}$ = fine particulate matter with an aerodynamic diameter of < 2.5 µm, SO_2 = sulfur dioxide, NO_2 = nitrogen dioxide, CO = carbon monoxide, O_3 = ozone, Min = minimum, Max = maximum.

Air pollution and meteorological data collected during the study period are shown in **Table 2**. The median concentrations of PM_{10}, $PM_{2.5}$, SO_2, NO_2, CO, O_3, and daily average temperature and relative humidity were 32.5 µg/m³, 18.5 µg/m³, 3.3 ppb, 21.2 ppb, 0.5 ppm, 19.8 ppb, 5.8°C and 65.2%, respectively. The correlation matrix between air pollutants, air temperature, and relative humidity during the study period is shown in **Supplementary Table 1**. All correlation coefficients were statistically significant ($P < 0.01$).

After setting the lag day from 0 to 7 days based on the confirmed date of COVID-19 diagnosis, a binomial logistic regression analysis was performed for each lag day. In each model, the effect of the concentration of air pollutants in the residence of confirmed COVID-19 patients on the occurrence of chemosensory dysfunction was presented as ORs and 95% CIs per IQR increase in each air pollutant.

The prevalence of chemosensory dysfunction increased 1.10-fold (95% CI, 1.04–1.16) as PM_{10} concentration increased by 22.4 µg/m³ and by 1.10-fold (95% CI, 1.03–1.16) as $PM_{2.5}$ increased by 16.3 µg/m³ on the day of diagnosis (Lag 0). For SO_2 concentration, an increase of 1.2 ppb led to increase in the occurrence of chemosensory dysfunction of 1.17-fold (95% CI, 1.10–1.25), and an increase of NO_2 concentration by 17.6 ppb, increased the number of symptomatic patients 1.31-fold (95% CI, 1.22–1.40). In addition, an increase of 0.2 ppm in the CO concentration on the day of diagnosis increased, led to an increase in occurrence of chemosensory dysfunction of 1.19 times (95% CI: 1.11–1.26). In contrast, as the O_3 concentration on the day of diagnosis increased by 13.5 ppb, the occurrence of chemosensory dysfunction decreased 0.78-fold (95% CI, 0.72–0.84).

For PM_{10} and $PM_{2.5}$, we found that the concentration up to 2 days before diagnosis of COVID-19 affected the occurrence of chemosensory dysfunction, and the concentration of SO_2, NO_2, CO and O_3 at least 7 days before the diagnosis affected chemosensory dysfunction (**Table 3**).

The effect of air pollutants on the development of chemosensory dysfunction was similar between the sexes (**Supplementary Fig. 1**). In addition, this effect was slightly greater in the older group than in the younger group (**Supplementary Fig. 2**).

JKMS

Table 3. The lag effects of air pollutants for chemosensory dysfunction in the binomial logistic regression model by lag time

Lag time, days	PM_{10} (per IQR)	$PM_{2.5}$ (per IQR)	SO_2 (per IQR)	NO_2 (per IQR)	CO (per IQR)	O_3 (per IQR)
Lag 0	**1.10 (1.04–1.16)**	**1.10 (1.03–1.16)**	**1.17 (1.10–1.25)**	**1.31 (1.22–1.40)**	**1.19 (1.11–1.26)**	**0.78 (0.72–0.84)**
Lag 1	**1.09 (1.02–1.15)**	**1.10 (1.04–1.17)**	**1.19 (1.11–1.27)**	**1.31 (1.23–1.40)**	**1.21 (1.14–1.28)**	**0.78 (0.73–0.84)**
Lag 2	**1.07 (1.00–1.13)**	**1.06 (1.00–1.12)**	**1.16 (1.10–1.23)**	**1.29 (1.20–1.38)**	**1.19 (1.12–1.16)**	**0.75 (0.70–0.81)**
Lag 3	1.00 (0.93–1.06)	0.98 (0.92–1.05)	**1.13 (1.06–1.21)**	**1.16 (1.09–1.24)**	**1.08 (1.02–1.07)**	**0.84 (0.78–0.90)**
Lag 4	0.97 (0.91–1.03)	0.96 (0.91–1.02)	**1.10 (1.03–1.17)**	**1.10 (1.02–1.17)**	1.02 (0.96–1.08)	**0.87 (0.81–0.94)**
Lag 5	1.01 (0.96–1.07)	1.00 (0.94–1.06)	**1.12 (1.04–1.19)**	**1.11 (1.03–1.18)**	1.06 (1.00–1.13)	**0.90 (0.84–0.97)**
Lag 6	1.03 (0.98–1.09)	1.02 (0.96–1.08)	**1.13 (1.06–1.20)**	**1.14 (1.07–1.22)**	**1.10 (1.04–1.17)**	**0.86 (0.80–0.92)**
Lag 7	1.03 (0.97–1.08)	1.01 (0.96–1.07)	**1.13 (1.06–1.20)**	**1.16 (1.09–1.24)**	**1.12 (1.06–1.18)**	**0.83 (0.77–0.89)**

Values are presented as odds ratio (95% confidence interval).
Bold values indicate statistically significant.
PM_{10} = fine particulate matter with an aerodynamic diameter of < 10 μm, $PM_{2.5}$ = fine particulate matter with an aerodynamic diameter of < 2.5 μm, SO_2 = sulfur dioxide, NO_2 = nitrogen dioxide, CO = carbon monoxide, O_3 = ozone, IQR = interquartile rage.

DISCUSSION

In this study, the air pollution indicators that increase the occurrence of chemosensory dysfunction due to COVID-19 were identified as PM_{10}, $PM_{2.5}$, SO_2, NO_2, CO. To date, few studies have reported on the relationship between chemosensory dysfunction caused by SARS-CoV-2 infection and air pollutants. Zhang et al.[16] have reported that long-term exposure to increasing concentrations of $PM_{2.5}$ exposure was associated with anosmia. However, to our knowledge, studies on the relationship between short-term exposure to air pollutants and chemosensory dysfunction in COVID-19 patients have not yet been reported.

The results of the present study show that the PM_{10} and $PM_{2.5}$ concentrations up to 2 days before diagnosis had an important effect on chemosensory dysfunction, and of the level of SO_2, NO_2, and CO at least one week before the diagnosis was related to the chemosensory dysfunction. Unfortunately, it is difficult to explain the reason for this difference in this study.

Unlike the case of other pollutants, it was found that higher O_3 concentrations significantly reduced the incidence of chemosensory dysfunction. Although a definite explanation is not clear for this result, a possible reason is that O_3 has anti-inflammatory effect. O_3 is known to exhibit its strong anti-inflammatory effect by inhibiting nucleotide-binding and oligomerization domain-like receptors protein 3 inflammasome, which plays an important role in the inflammatory response in various diseases.[17] In addition, because the activity of ACE2 receptor inhibits by nuclear factor erythroid 2-related factor 2 (Nrf2)[18] and O_3 induces the rapid activation of Nrf2,[19] there is a possibility that increased O_3 concentration induced anti-inflammatory effects on olfactory nerves. However, since these mechanisms are derived from the effects of high O_3 concentration at the ppm level, further studies are needed on the effects of O_3 at atmospheric concentration.

In this study, the rate of occurrence of chemosensory dysfunction was very low in early 2020, when the domestic COVID-19 epidemic began, and it gradually increased toward the latter half of the study. Therefore, Korea recommended that chemosensory dysfunction must be included in the response guideline for preventing the spread of COVID-19 infection at public and multi-purpose facilities after May 11, 2020. There is a possibility that in the previous period, the conditions of patients with COVID-19 infection would not have been investigated for symptoms other than those that the patients voluntarily reported. This may be the reason for the low incidence of chemosensory dysfunction in Daegu city, where there was the first wave of the COVID-19 pandemic occurred from February to March 2020.

Another reason is the changes in the virus epidemic patterns with time. At the beginning of the epidemic, the D614 mutant virus, which had little affinity for the ACE2 receptor, was prevalent, and as time passed, the epidemic of the D614G mutant virus started. Several recent studies have reported that the D614G mutant virus shows a relatively high affinity for ACE2 and increases loss of smell. The number of cases of mutant virus infection has been reported to have increased due to the D614G mutant confirmed case introduced into Korea from Itaewon club or Seoul Sarang Jeil Church from May to June 2020.[20-22]

The proportion of patients with chemosensory dysfunction in this study was 3.2%, which was slightly lower than the proportion of patients with symptoms in other studies. According to the results of a systematic review published by Boscutti et al.,[23] the proportion of chemosensory dysfunction among confirmed COVID-19 patients was 0–98%, showing a very wide range of prevalence depending on the study design. The proportion of symptomatic patients is highly likely to vary depending on the race, lifestyle, and environment of the patients. In addition, considering the lack of formal quantitative chemosensory testing, the frequency of prevalence can be also estimated to vary greatly depending on the survey method. Moreover, the data used in this study may have been underreported in comparison with the data for research purposes because they were based on the national reporting system.

Sex-related trends among symptomatic patients have been also reported to differ among studies. While some studies reported that the proportion of symptomatic patients was higher among women,[24,25] the results of another study showed that the incidence of chemosensory dysfunction is generally higher in men because women are known to have relatively better olfactory function than men.[23] In this study, the effects of air pollutants on the development of chemosensory dysfunction was similar between the sexes.

The results on the association between age and chemosensory dysfunction due to air pollution are controversial. Our results showed that the effect of air pollution on chemosensory dysfunction was slightly greater in the older group than in the younger group. Since chemosensory dysfunction declines while susceptibility to air pollution increases with age, our results are consistent with other studies, in which age was a determinant of chemosensory dysfunction.[16,26] However, the reduced occurrence of chemosensory dysfunction with increasing age has been also reported in some other studies.[24,25,27,28] Although the exact cause underlying this trend is not yet known, the prevalence or incidence may have been underestimated because the elderly are often unaware of their sensory abnormalities. In addition, the younger the age group, the more time they spend outside, so exposure to air pollutants related to the outbreak of COVID-19 may be relatively high in younger patients. However, further research is needed to confirm this hypothesis.

Our data suggest that, to reduce the prevalence of chemosensory dysfunction due to COVID-19 infection, exposure to pollutants should be minimized by staying indoors and wearing masks in outdoor environments.

This study had some limitations. First, due to the limited secondary data, information for factors such as smoking history and access to medical services that could affect disease occurrence was not available; therefore, regional data was included as a correction variable in the regression model. Second, the exposure amount of air pollutants used in this study is the regional concentration determined using the national measurement network, not the individual exposure concentration. Because each individual has different outdoor activity

hours and even those who use the same measurement network data may show differences in exposure depending on the area of residence, it is necessary to evaluate individual exposure for a more accurate relevance assessment.

Nevertheless, this study has the following significance. Many studies to evaluate the relationship between air pollution and disease occurrence have been conducted as ecological studies at the regional level. However, this study has the advantage of overcoming ecological errors by analyzing the effects of air pollutant exposure in 2020 on the chemosensory dysfunction of confirmed COVID-19 patients as individual data. In addition, this is the first study to evaluate the relationship between chemosensory dysfunction and air pollution for all confirmed cases of COVID-19 in Korea in 2020.

To summarize, this study showed that when the concentration of air pollutants such as SO_2, NO_2, and CO for at least one week is high, there is a high risk of developing chemosensory dysfunction due to COVID-19 infection. This finding underscores the need to actively prevent exposure to air pollution and prevent COVID-19 infection. In addition, policies that regulate activities and products that create high amounts of harmful environmental wastes may help in promoting better health for all during COVID-19 pandemic.

ACKNOWLEDGMENTS

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Correlation matrix between air pollutants and meteorological factors on the day of diagnosis of coronavirus disease 2019

Click here to view

Supplementary Fig. 1
Associations between exposure to air pollutants (lags 0–7 days before coronavirus disease 2019 diagnosis) and the risk of chemosensory dysfunction after adjusting for age, standardized smoking rate, number of outpatient visits, and daily average temperature and relative humidity according to sex. Odds ratio was calculated as the interquartile range increase in air pollution.

Click here to view

Supplementary Fig. 2
Associations between exposure to air pollutants (lags 0–7 days before coronavirus disease 2019 diagnosis) and the risk of chemosensory dysfunction after adjusting for sex, standardized smoking rate, number of outpatient visits, daily average temperature and relative humidity according to the age group. Odds ratio was calculated as the interquartile

range increase in air pollution. Older group, median age ≥ 46 years; younger group, median age < 46 years.

Click here to view

REFERENCES

1. Park WB, Kwon NJ, Choi SJ, Kang CK, Choe PG, Kim JY, et al. Virus isolation from the first patient with SARS-CoV-2 in Korea. *J Korean Med Sci* 2020;35(7):e84.
   PUBMED | CROSSREF

2. Suzaki I, Kobayashi H. Coronavirus disease 2019 and nasal conditions: a review of current evidence. *In Vivo* 2021;35(3):1409-17.
   PUBMED | CROSSREF

3. Cazzolla AP, Lovero R, Lo Muzio L, Testa NF, Schirinzi A, Palmieri G, et al. Taste and smell disorders in COVID-19 patients: role of IL-6. *ACS Chem Neurosci* 2020;11(17):2774-81.
   PUBMED | CROSSREF

4. Borro M, Di Girolamo P, Gentile G, De Luca O, Preissner R, Marcolongo A, et al. Evidence-based considerations exploring relations between SARS-CoV-2 pandemic and air pollution: involvement of PM2.5-mediated up-regulation of the viral receptor ACE-2. *Int J Environ Res Public Health* 2020;17(15):5573.
   PUBMED | CROSSREF

5. Li HH, Liu CC, Hsu TW, Lin JH, Hsu JW, Li AF, et al. Upregulation of ACE2 and TMPRSS2 by particulate matter and idiopathic pulmonary fibrosis: a potential role in severe COVID-19. *Part Fibre Toxicol* 2021;18(1):11.
   PUBMED | CROSSREF

6. Lee Y, Min P, Lee S, Kim SW. Prevalence and duration of acute loss of smell or taste in COVID-19 patients. *J Korean Med Sci* 2020;35(18):e174.
   PUBMED | CROSSREF

7. von Bartheld CS, Hagen MM, Butowt R. Prevalence of chemosensory dysfunction in COVID-19 patients: a systematic review and meta-analysis reveals significant ethnic differences. *ACS Chem Neurosci* 2020;11(19):2944-61.
   PUBMED | CROSSREF

8. Okada Y, Yoshimura K, Toya S, Tsuchimochi M. Pathogenesis of taste impairment and salivary dysfunction in COVID-19 patients. *Jpn Dent Sci Rev* 2021;57:111-22.
   PUBMED | CROSSREF

9. Seo MY, Seok H, Hwang SJ, Choi HK, Jeon JH, Sohn JW, et al. Trend of olfactory and gustatory dysfunction in COVID-19 patients in a quarantine facility. *J Korean Med Sci* 2020;35(41):e375.
   PUBMED | CROSSREF

10. Tung NT, Cheng PC, Chi KH, Hsiao TC, Jones T, BéruBé K, et al. Particulate matter and SARS-CoV-2: a possible model of COVID-19 transmission. *Sci Total Environ* 2021;750:141532.
    PUBMED | CROSSREF

11. Lembo R, Landoni G, Cianfanelli L, Frontera A. Air pollutants and SARS-CoV-2 in 33 European countries. *Acta Biomed* 2021;92(1):e2021166.
    PUBMED | CROSSREF

12. Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Persistent symptoms 1.5-6 months after COVID-19 in non-hospitalised subjects: a population-based cohort study. *Thorax* 2021;76(4):405-7.
    PUBMED | CROSSREF

13. Hutton JL, Baracos VE, Wismer WV. Chemosensory dysfunction is a primary factor in the evolution of declining nutritional status and quality of life in patients with advanced cancer. *J Pain Symptom Manage* 2007;33(2):156-65.
    PUBMED | CROSSREF

14. Sehanobish E, Barbi M, Fong V, Kravitz M, Sanchez Tejera D, Asad M, et al. COVID-19-induced anosmia and ageusia are associated with younger age and lower blood eosinophil counts. *Am J Rhinol Allergy* 2021;35(6):830-9.
    PUBMED | CROSSREF

15. Meini S, Suardi LR, Busoni M, Roberts AT, Fortini A. Olfactory and gustatory dysfunctions in 100 patients hospitalized for COVID-19: sex differences and recovery time in real-life. *Eur Arch Otorhinolaryngol* 2020;277(12):3519-23.
    PUBMED | CROSSREF

16. Zhang Z, Rowan NR, Pinto JM, London NR, Lane AP, Biswal S, et al. Exposure to particulate matter air pollution and anosmia. *JAMA Netw Open* 2021;4(5):e2111606.
    PUBMED | CROSSREF

17. Yu G, Bai Z, Chen Z, Chen H, Wang G, Wang G, et al. The NLRP3 inflammasome is a potential target of ozone therapy aiming to ease chronic renal inflammation in chronic kidney disease. *Int Immunopharmacol* 2017;43:203-9.
    PUBMED | CROSSREF

18. Sagai M, Bocci V. Mechanisms of action involved in ozone therapy: Is healing induced via a mild oxidative stress? *Med Gas Res* 2011;1(1):29.
    PUBMED | CROSSREF

19. Pecorelli A, Bocci V, Acquaviva A, Belmonte G, Gardi C, Virgili F, et al. NRF2 activation is involved in ozonated human serum upregulation of HO-1 in endothelial cells. *Toxicol Appl Pharmacol* 2013;267(1):30-40.
    PUBMED | CROSSREF

20. von Bartheld CS, Mathew D, Butowt R. New study on prevalence of anosmia in COVID-19 implicates the D614G virus mutation as a major contributing factor to chemosensory dysfunction. *Eur Arch Otorhinolaryngol* 2021;278(9):3593-4.
    PUBMED | CROSSREF

21. Meng X, Pan Y. COVID-19 and anosmia: the story so far. *Ear Nose Throat J* 2021;1455613211048998.
    PUBMED | CROSSREF

22. Ozono S, Zhang Y, Ode H, Sano K, Tan TS, Imai K, et al. SARS-CoV-2 D614G spike mutation increases entry efficiency with enhanced ACE2-binding affinity. *Nat Commun* 2021;12(1):848.
    PUBMED | CROSSREF

23. Boscutti A, Delvecchio G, Pigoni A, Cereda G, Ciappolino V, Bellani M, et al. Olfactory and gustatory dysfunctions in SARS-CoV-2 infection: a systematic review. *Brain Behav Immun Health* 2021;15:100268.
    PUBMED | CROSSREF

24. Strak M, Janssen N, Beelen R, Schmitz O, Karssenberg D, Houthuijs D, et al. Associations between lifestyle and air pollution exposure: potential for confounding in large administrative data cohorts. *Environ Res* 2017;156:364-73.
    PUBMED | CROSSREF

25. Galluzzi F, Rossi V, Bosetti C, Garavello W. Risk factors for olfactory dysfunctions in patients with SARS-CoV-2 infection. *Neuroepidemiology* 2021;55(2):154-61.
    PUBMED | CROSSREF

26. Schlosser RJ, Desiato VM, Storck KA, Nguyen SA, Hill JB, Washington BJ, et al. A community-based study on the prevalence of olfactory dysfunction. *Am J Rhinol Allergy* 2020;34(5):661-70.
    PUBMED | CROSSREF

27. Schikowski T, Sugiri D, Reimann V, Pesch B, Ranft U, Krämer U. Contribution of smoking and air pollution exposure in urban areas to social differences in respiratory health. *BMC Public Health* 2008;8(1):179.
    PUBMED | CROSSREF

28. Schiffman SS. Perception of taste and smell in elderly persons. *Crit Rev Food Sci Nutr* 1993;33(1):17-26.
    PUBMED | CROSSREF