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Natural and socio-environmental factors in the transmission of COVID-19: a comprehensive analysis of epidemiology and mechanisms

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Abstract

Purpose of review There are significant differences in the transmission rate and mortality rate of COVID-19 under environmental conditions such as seasons and climates. However, the impact of environmental factors on the role of the COVID-19 pandemic and the transmission mechanism of the SARS-CoV-2 is unclear. Therefore, a comprehensive understanding of the impact of environmental factors on COVID-19 can provide innovative insights for global epidemic prevention and control policies and COVID-19 related research. This review summarizes the evidence of the impact of different natural and social environmental factors on the transmission of COVID-19 through a comprehensive analysis of epidemiology and mechanism research. This will provide innovative inspiration for global epidemic prevention and control policies and provide reference for similar infectious diseases that may emerge in the future.

Recent findings Evidence reveals mechanisms by which natural environmental factors influence the transmission of COVID-19, including (i) virus survival and transport, (ii) immune system damage, (iii) inflammation, oxidative stress, and cell death, and (iiii) increasing risk of complications. All of these measures appear to be effective in controlling the spread or mortality of COVID-19: (1) reducing air pollution levels, (2) rational use of ozone disinfection and medical ozone therapy, (3) rational exposure to sunlight, (4) scientific ventilation and maintenance of indoor temperature and humidity, (5) control of population density, and (6) control of population movement. Our review indicates that with the continuous mutation of SARS-CoV-2, high temperature, high humidity, low air pollution levels, and low population density more likely to slow down the spread of the virus.

Keywords COVID-19, Nature environmental factor, Social environmental factor, Epidemiology, Mechanism research

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Introduction

Coronavirus disease 2019 (COVID-19) is defined as a disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which is an emerging respiratory infection. COVID-19 can occur through close contact with an infected person. The disease is characterized by high transmission rate, long incubation period, and global spread. On 11 March 2020, this disease was declared a global pandemic by the World Health Organization (WHO) [1]. The outbreak of COVID-19 has caused many threats and dangers to human health, including increased mortality and morbidity globally [2, 3]. The COVID-19 pandemic is challenging the world economy and health systems and demonstrates the extent of global interdependence and the need to address global health threats [4].

Current research on COVID-19 mainly focuses on vaccines, viruses, hosts and drugs [5]. In contrast, research on the impact of environmental factors on COVID-19 needs to be further carried out. The incidence of many similar infectious diseases showed seasonal patterns, including human coronaviruses [6]. COVID-19 is no exception and may have seasonal epidemic peaks. Therefore, understanding which environmental factors influence COVID-19 can allow planning and implementing public health interventions and capacities to reduce the impact of the disease. It will provide innovative inspiration for global epidemic prevention and control policies and provide reference for similar infectious diseases that may emerge in the future.

Although SARS-CoV-2 transmission has been recorded in almost all countries, there is significant spatial and temporal heterogeneity in transmission dynamics, morbidity and mortality across countries, regions and even communities [7]. Many studies have investigated the correlation between this spatial and temporal heterogeneity and environmental factors, including natural environmental factors and social environmental factors [8]. Direct or indirect evidence shows that these environmental factors have an impact on the spread and development of COVID-19 [9].

This research is used in Scopus, ISI scientific network and PubMed database ("climate" OR "climate change" OR "temperature" OR "precipitation" OR "relative humidity" OR "wind speed" OR "sunlight" OR "wind speed" OR “water resources” OR “solar radiation” OR “social environment factor” OR “air pollution” OR “PM2.5” OR “PM10” OR “ozone” OR “NO_2” OR “CO” OR “wastewater” OR “heavy metal pollution” OR “sociodemographic characteristics” OR “local policies” OR “socioeconomic activity”) and ("COVID" OR "Coronavirus disease 2019" OR "COVID-19" OR "SARS-CoV-2" OR "Novel Coronavirus" OR "COVID-19 transmission" OR " Novel Coronavirus transmission" OR "COVID-19 confirm case"). Inclusion criteria are all relevant manuscripts that assess the impact of environmental factors on the number of cases and incidence rate of COVID-19. Exclusion criteria include comments, letters, editorials, conference abstracts, and low-quality research.

This review summarizes the impact of environmental factors on the transmission of COVID-19 and summarizes studies from epidemiological evidence to mechanisms. We divide environmental factors into natural environmental factors and social environmental factors. Natural environmental factors include air pollution, temperature, humidity, wind speed, rainfall, solar radiation, soil and water resources. Social environmental factors include sociodemographic characteristics, local policies and socioeconomic activity. Finally, there is a discussion of the potential future directions in this field. Critical assessments of these relationships can enhance estimates of the risk of similar infectious diseases from environmental exposures and guide the design of interventions to slow the spread of the virus and protect vulnerable populations from infection. This will provide innovative inspiration for global epidemic prevention and control policies and provide reference for similar infectious diseases that may emerge in the future.

Natural environment factors and transmission of COVID-19

Native environment factor

Temperature and humidity

The relationship between viral infections and meteorological conditions has been of concern in the past. Researchers from China looked at the link between temperature and humidity in more than 3750,000 confirmed COVID-19 cases from 185 countries. It found that 60.0% of confirmed COVID-19 cases occurred in places with temperatures between 5℃ and 15℃, with a peak of 11.54℃. In addition, about 73.8% of confirmed cases are concentrated in areas with absolute humidity of 3 g/m^3 to 10 g/m^3 [10]. In Japan, researchers conducted a longitudinal cohort study of 6,529 confirmed COVID-19 cases across 28 geographical areas. The results showed that the increase of the COVID-19 epidemic was significantly correlated with the increase of daily temperature or sunshine duration [11]. Haque and Rahman found that high temperature and high humidity significantly reduced the spread of COVID-19, respectively. In Bangladesh, more than four-fifths (84.2%) of the total cases were clustered within the average temperature range (26–28℃) [12]. This is consistent with the results of a previous ecological study, which found that the optimal ambient temperature associated with SARS cases was between 16℃ and 28℃, based on data from Hong Kong, Guangzhou, Beijing and

Taiyuan [13]. The seasonal cycle of respiratory viral diseases has been widely recognized for thousands of years. The temporal trends of COVID-19 transmission presented a periodic fluctuation and reflected the seasonal changes. In terms of time series, in line with the seasons in Brazil, the average temperature and relative humidity from March to May (autumn) had a significant positive effect on new cases, while the months from June to August (winter) and September to November (spring) had a negative effect [14].

In a systematic review of 17 studies has found that climate parameters may be an important factor in the spread of COVID-19. Cold and dry conditions enhance the spread of the virus [15]. A systematic review of 62 publications were published between December 2019 and February 2021 on the association between climate factors and the spread of COVID-19, found consistent results that high temperatures may have significantly influenced the spread of COVID-19 and suppressed the pandemic [16]. Yuan et al. found that they may be negatively associated with daily new cases of COVID-19 in 127 countries when temperature, relative humidity, and wind speed are lower than 20 °C, 70%, and 7 m/s, respectively. In a follow-up study, it found to be inversely associated with daily new cases of COVID-19 in 188 countries when temperatures and relative humidity below 21 °C and 64%, respectively. And in these two studies, the researchers found that temperature and humidity were negatively correlated with the daily number of new COVID-19 cases and deaths [17, 18]. In India, researchers found that most COVID-19 cases had surface temperatures between 24 and 30℃ and relative humidity between 50 and 80 percent, which is highly dependent on relative humidity at certain temperatures [19]. However, some studies [20] report that SARS-CoV-2 transmission is ineffective with increasing temperature. For the role of meteorological parameters, this contradictory discovery is mainly due to the difference in analysis methods and limitation in data availability of each study.

Solar radiation, sunlight exposure, and wind speed

Other climatological factors can also affect the spread of SARS-CoV-2, previous evidence shows that solar radiation and wind speed also affect the spread of infectious diseases [21, 22]. For example, in the tropical state of Rio de Janeiro in Brazil, studies have found that high solar radiation can be shown to be a major climatic factor in curbing the spread of COVID-19. Solar radiation was positively correlated with the infection of COVID-19. There was a significant negative correlation between higher wind speed and lower incidence of COVID-19 [23]. Researchers in Iran found that areas with low wind speeds and exposure to solar radiation had higher rates of infection, which helped the virus survive [24]. In a descriptive observational cross-sectional study conducted in France, a significant negative association between sun exposure and COVID-19 mortality was observed [25]. Another study analyzed the correlation between the meteorological parameters and the transmission of COVID-19 in Baghdad, the capital of Iraq. The results show that temperature, wind speed and solar radiation are the primary meteorological parameters leading to the spread of COVID-19 in Baghdad and are related to the confirmed cases and deaths of COVID-19 [26]. But a study on the correlation between solar radiation exposure and the COVID-19 pandemic in Jakarta, Indonesia, found different results. The study found no significant correlation between sun exposure and morbidity and death in patients with COVID-19. Sunlight was significantly associated with recovery from COVID-19 [27]. In the latest study, Al-Khateeb et al. compared the association between multiple regional weather conditions in the Northern hemispheres, Southern hemispheres, and Irbid, Jordan and COVID-19 transmission, found that the relationship between wind speed and spread of COVID-19 was oscillatory and insignificant on a worldwide [28]. Statistical results may not confirm a specific causal relationship between exposure to solar UV radiation and disease variables such as morbidity and mortality [29].

Water resource

SARS-CoV-2 deposited on the surface of objects can be washed into the surface runoff by rainfall. Although the waterborne transmission of COVID-19 has not been confirmed, the potential risk cannot be ignored. Research therefore needs to answer whether hydrological conditions (such as river length, lake area, precipitation and volume of water resources) are related to COVID-19 outbreaks. For example, the researchers investigated the associations between hydrological factors such as lake area, river length, precipitation and volume of water resources in 30 regions of China and the incidence of COVID-19. The results showed that the number of confirmed COVID-19 cases was moderately correlated with river length and precipitation, but weakly correlated with water resources [30]. Precipitation had been analyzed in studies in Indonesia, the United States and Brazil, had not been found to be associated with COVID-19 [31–33]. However, other studies had also found that precipitation is positively correlated with the spread of COVID-19. Countries with higher rainfall showed an increase in disease transmission. On average, there were 56.01 additional cases per inch/day [33].

Environmental pollution factor and transmission of COVID-19

Air pollution

Epidemiologic evidence shows a strong link between air pollution and COVID-19, contributing significantly to the transmission and severity of COVID-19 [34, 35]. In the United States, researchers used ecological regression analysis to examine the relationship between long-term (2000–2016) average PM2.5 concentrations and COVID-19 mortality over 3,089 counties. After accounting for many county-level confounders, researchers found that a 1 μg per m^3 increase in PM2.5 was associated with an 11% increase in county-level COVID-19 mortality rate [36]. The same results were found in another study, in which researchers found a significant positive correlation between 2016 average PM2.5 concentrations in 3,110 US counties and COVID-19 mortality [37]. An ecological study in Italy found a positive correlation between PM2.5 concentrations and excess mortality associated with COVID-19 in Northern Italy. A one-unit increase in PM2.5 concentration (μg/m^3) is associated with a 9% increase in COVID-19 related mortality [38]. Several ecological studies in other countries such as China, UK and Netherlands had found the same results, with areas with poorer air quality are more likely to have elevated COVID-19 incidence and mortality [39–41].

Short-term exposure to air pollution may also affect COVID-19, with multiple studies finding that air pollution may affect recovery time, mortality, morbidity, and emergency department visits [42]. For example, researchers conducted a case-crossover study of 78,255 emergency department visits for COVID-19 in two Canadian provinces. The study found a significant correlation between PM2.5 and emergency department visits for COVID-19 [43]. In Changsha, China, Liu et al. found that long recovery duration among COVID-19 patients was positively correlated with short-term exposure to PM2.5, NO_2, and CO [44]. The researchers also found that COVID-19 patients with both Delta and Omicron had an increased chance of developing early respiratory COVID-19 manifestations after short-term exposure to air pollution [45].

In addition to particulate matter (PM), which has been widely studied, a number of studies have also involved carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O^3) and other air pollutants [46]. In a comparative study of the impact of air pollution on COVID-19 in multiple countries, a correlation between pollutant gases and COVID-19 risk was found in the United States, Italy and Spain, while in China the relationship was negative. Factors in air pollution have different associations with COVID-19 risk [47]. Another study looked at 446,440 COVID-19 cases, covering 4,609 census tracts in southern California. The pooled RR (95%CI) for the incidence of COVID-19 associated with 1-year exposure to NO_2 and O^3 were 1.09 (1.02, 1.17) per 3.2 ppb and 1.06 (1.00, 1.12) per 5.5 ppb respectively [48]. In Los Angeles, long-term exposure to NO_2 has been associated with an increased risk of COVID-19 cases and mortality. The researchers found that an 8.7 ppb increase in annual mean NO_2 concentrations was associated with a 16–31% increase in the rate of COVID-19 cases and a 35–60% increase in mortality [49].

Wastewater

The waterborne transmission of COVID-19 has not been confirmed. Early in the SARS-CoV-2 outbreak, it was reported that live SARS-CoV-2 could be isolated from the feces and urine of COVID-19 patients [50]. And according to the experience accumulated during the SARS epidemic, sewage systems could also be contaminated by the virus [51]. Different concentrations of SARS-CoV-2 have been detected in wastewater in the Netherlands, Belgium, Australia, and the United States [52–54]. To date, there have been no studies in the public domain on the persistence and survivability of SARS-CoV-2 in water or wastewater. But a link between the virus and persistence and survival can be found from previous studies of coronaviruses. For example, human coronavirus 229E can survive for 7 days in water at 23 °C [55]. Researchers performed SARS-CoV-2 RNA detection by real-time RT-PCR and infectivity test on culture cells on three river samples in Milan, Italy. Real-time RT-PCR results showed positive, but infectivity was not effective [56].

Through the secondary utilization of wastewater and the disposal of medical waste, SARS-CoV-2 can enter the soil environment [57, 58]. In China, 20% of soil samples taken near hospitals receiving COVID-19 subjects and Wuhan sewage treatment plants recently tested positive for SARS-CoV-2 RNA, with abundance ranging from 205 to 550 copies/g [59]. Similar to the research status of viruses in water resources, the activity and infectivity of viruses in soil resources have not been widely studied and confirmed [60]. But there is no denying that the virus can seriously affect soil health, and improper handling will pose a threat to human and animal health.

Heavy metal pollution

Hydrosphere and pedosphere are essential natural environment factors. Since heavy metals are not biodegradable, heavy metal ions in water and in soil be biologically accumulated via the food chain towards the human body. Most heavy metals, such as arsenic (As), lead (Pb), mercury (Hg), and cadmium (Cd) are considered environmental pollutants [61]. Previous evidence suggested that heavy metal exposure is associated with

higher mortality from influenza or pneumonia [62]. In the laboratory, heavy metal exposure has been found to play a role in impaired mucociliary clearance, reduced barrier function, airway inflammation, oxidative stress, and apoptosis [63]. Exposure to these heavy metals after COVID-19 infection may increase the risk of severe COVID-19 through these abnormal or exaggerated immune responses [64]. Studies had found that exaggerated immune responses are associated with multiple organ system failure, COVID-19 hospitalization, and death [65].

Chronic exposure to As, Cd, Hg, and Pb has been associated with respiratory dysfunction and respiratory diseases [66]. Solenkova et al. reviewed English-speaking medical literature to find that Hg, Pb, Cd, and as are associated with cardiovascular disease of atherosclerotic origin [67]. In additional, epidemiologic studies have found that cumulative exposure to heavy metal mixtures is associated with obesity and its associated chronic diseases, such as hypertension and type 2 diabetes [68]. These diseases have a significant impact on COVID-19. For example, the most common comorbidities found in COVID-19 cases in clinical studies are hypertension, followed by diabetes. More comorbidities were associated with poorer clinical outcomes. Obesity and type 2 diabetes are risk factors for poor COVID-19 prognosis [69].

While it is true that heavy metals have impact on COVID-19 patients, there is a lack of direct data linking exposure to heavy metals to the risk and/or severity of COVID-19. In a retrospective analysis of 306 patients confirmed COVID-19 in China, researchers analyzed levels of essential and/or toxic metals (classes) in whole blood, depending on the severity and outcome of the disease. The results found that among severely ill patients, the death group had higher levels of chromium and cadmium and lower levels of arsenic compared to the recovery group [70]. One study found that COVID-19 patients with elevated levels of chromium, cadmium, mercury and lead in their urine had a poorer prognosis (severe and non-severe) [71].

Social environment factor and transmission of COVID-19

Evidence linking sociodemographic characteristics to transmission of COVID-19

Droplet or airborne transmission is the main route of SARS-CoV-2 transmission, and higher population density often leads to the long-term spread of COVID-19 [72]. In Malaysia, areas with a high number of residents and high population density have a greater number of cases in proportion to the population of the area. The correlation between COVID-19 cases and population density was strongest in the central region [73]. Another study using long-term data on the relationship between external demographic parameters such as total population, population density and weighted population density and the spread of COVID-19 in Malaysia found different results. The results showed that there was a strong and significant positive correlation between total population and COVID-19 cases. However, a weak positive relationship was found between density variables (population density and weighted population density) and the spread of COVID-19 [74]. But most studies show that increasing population density in turn leads to an increase in COVID-19 cases and deaths [75]. Population density is thought to have a more significant impact on COVID-19 than meteorological factors. For example, the researchers investigated the correlation of spread and decay durations of the COVID-19 pandemic in China, the United Kingdom, Germany, and Japan with temperature, humidity, and population density. The results showed that propagation duration and decay durations were significantly correlated with population density, and the effect of population density was more significant than that of meteorological factors [76]. The characteristics of the built environment at different spatial scales caused by different population parameters will also affect the prevention and spread of infectious diseases. Poor housing conditions and high building density can lead to problems with inadequate sanitation facilities, which will create an environment conducive to disease transmission [77]. In Hong Kong, China, for example, research had shown that high transport accessibility, dense high-rise buildings, higher density of commercial land, and a higher land use mix are associated with a higher risk of being visited by confirmed cases. More green space, higher median household income, and lower commercial land density were associated with a higher risk of housing with confirmed cases [78].

There are race-related health disparities in the COVID-19 pandemic, with higher morbidity and mortality rates among ethnic minorities. Black workers most affected by the outbreak are more likely to be employed in key industries, in occupations that involve frequent exposure to infections and close relationships with others [79]. But other studies had found little evidence that occupation affects infection rates. For example, infection rates among frontline healthcare workers have not been shown to be higher than those non frontline healthcare workers. The strongest risk factors associated with COVID-19 infection among health care workers were neighborhood infection rates and ethnicity [80]. In addition, risk factors for developing COVID-19 in adults include age and gender [81]. For example, Increased mortality from COVID-19 was significantly associated with higher rates of obesity in women and higher rates of smoking in men [82]. There is growing evidence that COVID-19 produces

more severe symptoms and higher mortality in men than in women [83]. As a vulnerable group with reduced immune system effectiveness, the elderly are often at a higher risk of infectious diseases [84]. Susceptibility to SARS-CoV-2 infection increases with age [85, 86].

Evidence linking local policies and socioeconomic activity to transmission of COVID-19

Person-to-person transmission is the main way of transmission of COVID-19. In response to the threat of the epidemic, many countries have introduced measures to restrict the movement of people. In Wuhan, China, for example, there was a significant decrease in new cases during the four-day lockdown. During that time, the increase in new cases dropped by about 50%, with the number of cases fluctuating on the fifth day and then rapidly decreasing [87]. The researchers investigated the movement of people and government restrictions as a function during successive waves of SARS-CoV-2 mutation in Canada. The results showed that in the first two years, government restrictions were high, and turnover was low, characterizing a 'seek-and-destroy' approach. After this phase, the highly transmissible Omicron (B.1.1.529) variant began circulating in NS at the end of the following year, leading to an increase in cases, hospitalizations, and deaths. During Omicron, although the transmissibility (26.41 times) and lethality (9.62 times) of the new variant increased, unsustainable government restrictions and declining public compliance led to increased population mobility [88]. In another cross-sectional study, containment and confinement were found to be significantly associated with overall mobility and were associated with a reduction in SARS-CoV-2 infection [89]. Lockdowns also reduce air pollution, and NO_2 concentrations can be used as environmental indicators to evaluate the effectiveness of lockdowns. In the United Kingdom, researchers found that exposure to NO_2 dropped significantly during lockdowns, while exposure to PM2.5 dropped relatively little [90]. In a Cochrane systematic review, 84 studies were analyzed and found that isolation or microbiological testing, or a combination of both, prevented further cases. These interventions may have a positive shift in the development of the epidemic, and case detection may improve [91]. It has also been reported that 100% use of masks combined with lockdown is a measure that can reduce the risk of additional waves [92]. Masks could be one of the main pillars in the fight against the virus [93]. Finally, with lockdown measures in place, maintaining adequate indoor air quality levels is critical to slowing airborne viruses [94].

Socioeconomic activity has also been the focus of many studies investigating the factors affecting COVID-19 [95]. Epidemics may accelerate during periods of economic activity, possibly because of an increase in the number of people traveling, followed by an increase in human contact. For example, studies had proved that international trade exceeded other common parameters used to prove the spread of COVID-19 due to economic, demographic, environmental and climatic factors [96]. The sum of international data on import and export trade can be a complex but appropriate indicator for measuring the underlying socioeconomic dynamics of geo-economic areas [96]. Another study examined the role of trade in the dynamics of epidemic spread within and between countries in three large European countries: Italy, France, and Spain. The findings suggest that the association between trade and outbreak severity appears to be supported by empirical evidence, potentially introducing new hypotheses to explain the dynamics of COVID-19 transmission within and between countries [97].

Mechanism of nature environmental factors influencing the SARS-CoV-2

Native environment factor

Temperature and humidity

As noted above, there is growing epidemiologic evidence that the risk of transmission of SARS-CoV-2 was influenced by temperature and humidity. Many studies at the molecular level may further confirm this idea. Temperature can promote changes in the molecular structure of biomacromolecules (i.e., nucleic acids, proteins, lipids) until affecting their function. In the case of proteins, temperature is known to induce changes in secondary and tertiary structures, resulting in structural alterations that alter their stability and their role in regulating cellular processes, signal transduction, and intrinsic enzyme properties [98]. For example, the researchers used molecular dynamics simulation (MD) to reveal the molecular basis of the effect of temperature on the SARS-CoV-2 spike glycoprotein. The results showed that temperature induced conformational change of S1 subunit of SARS-CoV-2 spike glycoprotein that remodel the internal hydrogen bonding structure and especially affected secondary structure of the main region of interaction (RBD) of the spike glycoprotein of SARS-CoV-2 with the human ACE2 receptor [99]. Relative humidity (RH) can be considered an extrinsic factor for viral stability, as it controls evaporation, which affects the size of viral droplets, their physical fate, and their chemical microenvironment [100]. Table 1 summarizes some key studies of the effects of temperature and humidity on SARS-CoV-2 survival on different substrates. We found that the virus can survive on many substrates, and the lower the temperature and humidity, the longer the half-life of the virus. In one study, the half-life of the SARS-CoV-2 virus at 4 ℃ was three times that at 22 ℃. One of the studies in the

Table 1 Study of temperature and humidity on the activity of SARS-CoV-2

Substrate	Virus	Virus titer	Type	Temperature (℃) and relative humidity (%)	Virus stability (hour (h))	Reference
Human-biological fluids	SARS-CoV-2	5×10^4 (TCID50)	USA-WA1/2020	25 °C and 70%	t1/2: 2.3–12.57 h	[104]
Human-biological fluids	SARS-CoV-2	5×10^4 (TCID50)	USA-WA1/2020	21 °C and 60%	t1/2: 5.23–16.74 h	[104]
Human-biological fluids	SARS-CoV-2	5×10^4 (TCID50)	USA-WA1/2020	13 °C and 66%	t1/2: 15.98–54.34 h	[104]
Human-biological fluids	SARS-CoV-2	5×10^4 (TCID50)	USA-WA1/2020	5 °C and 75%	t1/2: 33.37–121.83 h	[104]
Surfaces under indoor	SARS-CoV-2	5×10^4 (TCID50)	USA-WA1/2020	25 °C and 70%	t1/2: 2.54–5.58h	[105]
Surfaces under indoor	SARS-CoV-2	5×10^4 (TCID50)	USA-WA1/2020	21 °C and 60%	t1/2: 3.5–12.86h	[105] [105]
Surfaces under indoor	SARS-CoV-2	5×10^4 (TCID50)	USA-WA1/2020	13 °C and 66%	t1/2: 17.11–31.82h	[105]
Surfaces under indoor	SARS-CoV-2	5×10^4 (TCID50)	USA-WA1/2020	5 °C and 75%	t1/2: 47.94–121.78 h	[105]
Steel	Delta B.1.617.2	1.1×10^4 pfu	HCM/V/078	Room temperature and humidity	99% titre reduction (56h)	[106]
Steel	Omicron BA.1.1.529	2.3×10^4 pfu	HCM/V/127	Room temperature and humidity	99% titre reduction (42h)	[106]
Laboratory equipment	SARS-CoV-2	5μL	Patient in the catarrhal phase	4 °C	t1/2: 273.36 h (glass slides)	[107]
Laboratory equipment	SARS-CoV-2	5μL	Patient in the catarrhal phase	24 °C	t1/2: 70.32 h (glass slides)	[107]
Non-porous surfaces	SARS-CoV-2	4.97×10^7 (TCID50)	Betacoronavirus/Australia/SA01/2020	20 °C and 50%	t1/2: 1.68–2.74d;	[108]
Non-porous surfaces	SARS-CoV-2	4.97×10^7 (TCID50)	Betacoronavirus/Australia/SA01/2020	30 °C and 50%	t1/2: 10.5–32.7 h	[108]
Non-porous surfaces	SARS-CoV-2	4.97×10^7 (TCID50)	Betacoronavirus/Australia/SA01/2020	40 °C and 50%	t1/2: 1.4–3.0 h	[108]
Human-biological fluids	SARS-CoV-2	1×10^5 (TCID50)	USA-WA1/2020	4°C and 40%	t1/2: 3.3 h and 5.8 h	[109]
Human-biological fluids	SARS-CoV-2	1×10^5 (TCID50)	USA-WA1/2020	21 °C and 40%	t1/2: 3.1 h	[109]
Human-biological fluids	SARS-CoV-2	1×10^5 (TCID50)	USA-WA1/2020	27 °C and 85%	t1/2: 1.5 h	[109]
Cat-biological fluids	SARS-CoV-2	5×10^4 (TCID50)	USA-WA/2020 strain	25 °C and 70%	t1/2: 2.84–12.74 h	[110]
Cat-biological fluids	SARS-CoV-2	5×10^4 (TCID50)	USA-WA/2020 strain	21 °C and 60%	t1/2: 2.71–8.1 h	[110]
Cat-biological fluids	SARS-CoV-2	5×10^4 (TCID50)	USA-WA/2020 strain	13 °C and 66%	t1/2: 7.42–18.38 h	[110]
Sheep-biological fluids	SARS-CoV-2	5×10^4 (TCID50)	USA-WA/2020 strain	25 °C and 70%	t1/2: 4.16–6.64 h	[110]
Sheep-biological fluids	SARS-CoV-2	5×10^4 (TCID50)	USA-WA/2020 strain	21 °C and 60%	t1/2: 6.10–9.33 h	[110]
Sheep-biological fluids	SARS-CoV-2	5×10^4 (TCID50)	USA-WA/2020 strain	13 °C and 66%	t1/2: 9.04–99.95 h	[110]
Polypropylene	SARS-CoV-2	1×10^5 (TCID50)	HCoV-19 nCoV-WA1-2020	10 °C and 40%	t1/2: 26.55 h	[111]
Polypropylene	SARS-CoV-2	1×10^5 (TCID50)	HCoV-19 nCoV-WA1-2020	10 °C and 65%	t1/2: 14.22 h	[111]
Polypropylene	SARS-CoV-2	1×10^5 (TCID50)	HCoV-19 nCoV-WA1-2020	10 °C and 85%	t1/2: 13.78 h	[111]
Polypropylene	SARS-CoV-2	1×10^5 (TCID50)	HCoV-19 nCoV-WA1-2020	22 °C and 40%	t1/2: 6.43 h	[111]
Polypropylene	SARS-CoV-2	1×10^5 (TCID50)	HCoV-19 nCoV-WA1-2020	22 °C and 65%	t1/2: 2.41 h	[111]
Polypropylene	SARS-CoV-2	1×10^5 (TCID50)	HCoV-19 nCoV-WA1-2020	22 °C and 85%	t1/2: 7.50 h	[111]

Table 1 (continued)

Substrate	Virus	Virus titer	Type	Temperature (℃) and relative humidity (%)	Virus stability (hour (h))	Reference
Polypropylene	SARS-CoV-2	1×10^5 (TCID50)	HCoV-19 nCoV-WA1-2020	27 °C and 40%	t1/2: 3.43 h	[111]
Polypropylene	SARS-CoV-2	1×10^5 (TCID50)	HCoV-19 nCoV-WA1-2020	27 °C and 65%	t1/2: 1.52 h	[111]
Polypropylene	SARS-CoV-2	1×10^5 (TCID50)	HCoV-19 nCoV-WA1-2020	27 °C and 85%	t1/2: 2.79 h	[111]
Polypropylene	SARS-CoV-2	1×10^5 (TCID50)	HCoV-19 nCoV-WA1-2020	10 °C	t1/2: 42.08 h	[111]
Polypropylene	SARS-CoV-2	1×10^5 (TCID50)	HCoV-19 nCoV-WA1-2020	22 °C	t1/2: 12.18 h	[111]
Polypropylene	SARS-CoV-2	1×10^5 (TCID50)	HCoV-19 nCoV-WA1-2020	27 °C	t1/2: 5.76 h	[111]

Abbreviations: t1/2 Half-life, *h* hour, *TCID50* tissue culture infectious dose 50%/mL

table confirms that the virus is least active at 40% relative humidity. It was also found that temperature seemed to have a greater effect on viral activity than relative humidity. However, neither temperature nor humidity can instantly inactivate the virus under normal conditions (Table 1). Some controlled studies of human nasal mucus and sputum, as well as viral aerosols, have shown that SARS-CoV-2 decayed faster at higher relative humidity [101]. This is consistent with evidence of influenza virus survival that influenza is best transmitted at low absolute humidity [102, 103].

Some innate immune responses are suppressed at low temperatures. The human upper respiratory tract is the first contact site of inhaled respiratory viruses and the body's first line of defense against these foreign pathogens. Once bacteria are detected in the front of the nose, the epithelial cells of the anterior nasal mucosa increase the release of extracellular vesicles (EVs) several times. These EVs enter the nasal mucus and have a direct antibacterial effect. At the same time, EVs can arm the more rear epithelial cells with immunoprotective proteins, inducing a four-fold increase in the production of nitric oxide in epithelial cells [112]. In a subsequent study, Huang et al. further explored the EVs biological mechanism, but found that the EVs-mediated potent antiviral immune defense function was impaired by cold exposure. At ambient conditions of 4.4 ℃, the number of EVs decreased by nearly 42%, while EVS-mediated functional delivery and the ability to neutralize viruses were weakened [113]. In addition, there is some research suggesting that cellular immune responses may also be affected by temperature and humidity. Mice airway epithelial cells initiated a stronger antiviral response at higher temperatures compared to lower temperatures [114], and mice exposed to low humidity conditions were more susceptible to influenza infection [115]. However, the effects of seasonal fluctuations in immune response on COVID-19 susceptibility and severity are still largely unknown. When the temperature is low, the human immune response is suppressed and the activity of the virus is increased, which promotes the spread of the COVID-19. When the temperature is high, it will change the conformation of SARS-CoV-2 spike glycoprotein S1 and reduce the activity of the virus, thus inhibiting the transmission of COVID-19. At 40% RH, the activity of the virus is lowest, thus inhibiting the spread of the novel coronavirus (Fig. 1A).

Solar radiation

Among the different climatological factors, sunlight has been found to play an important role in determining the spread of SARS-CoV-2. Sunlight contains a spectrum of ultraviolet A (UVA), UVB, and UVC. UV germicidal is a commonly used disinfection method, and it has previously been reported that UV can inactivate aerosolized coronaviruses [116]. Lorca-Oro et al. used UV-C (100-280 nm wavelength) to inactivate SARS-CoV-2 in a laboratory simulating hospital intensive care unit conditions. The results showed that after 12 min or more of UV-C exposure, the titer was reduced by ≥ 99.91% to ≥ 99.99%, and the minimum distance between the UV-C device and the SARS-CoV-2 dry sample was 100 cm [117]. Under simulated sunlight conditions in the laboratory, the researchers found that 90% of SARS-CoV-2 was inactivated after 19 min of exposure under simulated winter and autumn UV conditions, while some degree of inactivation was achieved after just 8 min under simulated summer conditions [118]. Several other studies have found similar results, inactivating 90% of SARS-CoV-2 every 6.8 min in simulated saliva and every 14.3 min

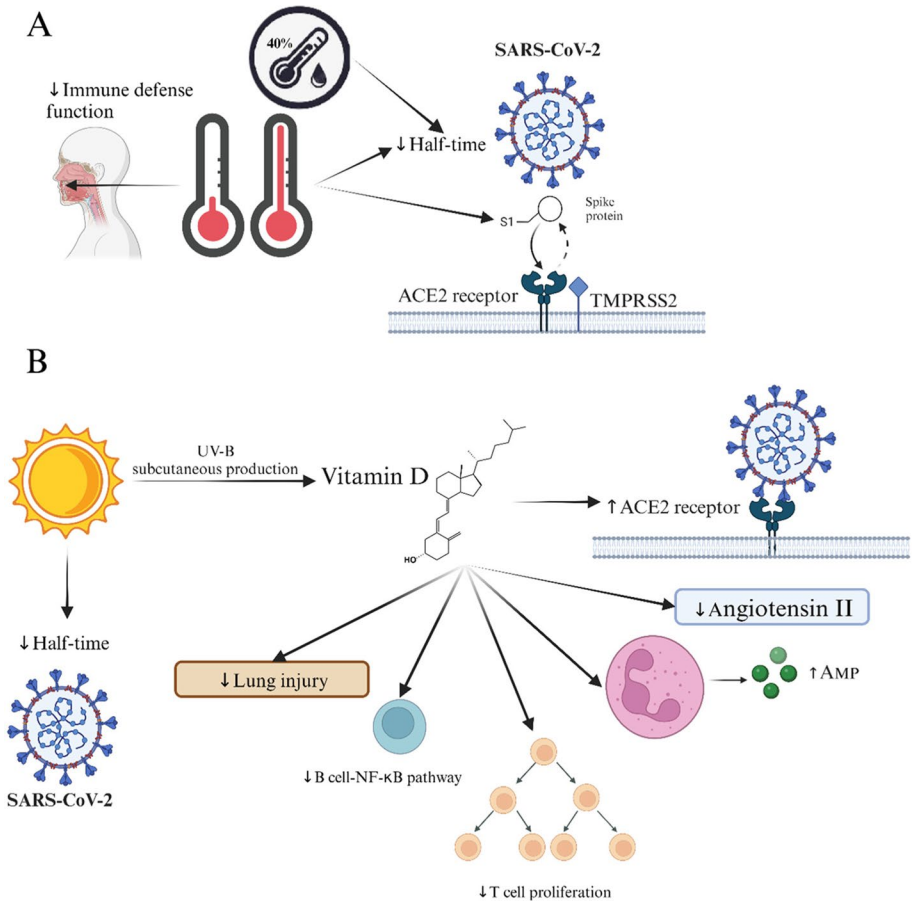

Fig. 1 Schematic diagram of the influence mechanism of natural environmental factors on the transmission of COVID-19. **A** Temperature. **B** Solar radiation. Promoting (upward arrow) or suppressing (downward arrow) the associated mechanism

in culture medium when exposed to simulated sunlight at the summer solstice (ultraviolet (UV) range: 280–400 nm) [119]. In the United States and most cities around the world, 90% or more of SARS-CoV-2 will be inactivated after 11–34 min of exposure to midday sunlight in the summer [120]. Observation of the above studies found that SARS-CoV-2 is inherently sensitive to UV. However, UVC can be absorbed by atmospheric ozone, and sunlight reaching the Earth's surface cannot directly eradicate SARS-CoV-2 through virus-killing activity [121].

UVB exposure is closely related to vitamin D synthesis. The body relies primarily on sun exposure to meet its vitamin D needs. UVB is absorbed by the 7-dehydrogenated cholesterol in the skin, causing it to be converted to pre-vitamin D3, which is quickly converted to vitamin D3 [122]. Significant increases in vitamin D can be achieved at very low UVB doses [123]. Solar radiation is highest in summer and at lower altitudes. Studies have found that in northern Europe, adequate vitamin D status can be achieved through summer sun exposure. In winter, however, the UVB radiation in the environment is too low to produce any vitamin D [124]. Regardless of skin type and ethnicity, there is almost no vitamin D synthesis in winter and spring at latitudes > 50°. Vitamin D deficiency is associated with the severity of COVID-19. In a meta-analysis, vitamin D deficiency was found to be more severe in severe cases compared to mild cases. Insufficient vitamin D levels increase hospitalization rates and COVID-19 mortality [125]. Vitamin D can reduce the risk of COVID-19 in the following ways (Fig. 1B): (1) Vitamin D helps immune cells produce antimicrobial peptides, which play an antibacterial and antiviral role [126]; (2) Vitamin D can inhibit T cell proliferation and the NF-κB pathway of B cells, and reduce the level of pro-inflammatory cytokines [127]; (3) Vitamin D can prevent the constriction response of pulmonary blood vessels in COVID-19 [128]; (4) Vitamin D alleviates lung injury by stimulating endothelial cell proliferation and migration, reducing epithelial cell apoptosis, and inhibiting TGF-β-induced epithelial-mesenchymal transformation [129]. More research is required to evaluate the mechanisms

whereby vitamin D might reduce the risk of COVID-19 [130].

Wind speed

There is strong evidence to support airborne transmission of SARS-CoV-2 [131, 132]. The World Health Organization (WHO) has identified inhalation of virus-carrying aerosols as the primary mode of transmission of SARS-CoV-2 over short and long distances. Airborne transmission is defined as less than 5 μm with > 1 to 2 m from an infected person [133]. Wind speed can strongly influence the transport of virus-carrying aerosols [134]. Aerosols tend to rise because they are warmer than ambient air and are confined indoors by surrounding walls and ceilings [135]. In open spaces, particles or droplets produced by normal breathing can only be transferred over short distances, and when sneezing or coughing, particles carry nearly the same distance, with differences only within a certain range. The greater the air flow outside, the greater the dispersion. One study found that the distance of breathing particles is 0.65m, the distance of coughing is 1.63m and the distance of sneezing is 2.86m [136]. In addition, studies have assessed the risk of spreading infectious particulate matter while chamber musicians play their instruments. It turns out that no matter the volume, pitch, or content of the play, it did not extend the range of the air flow [137]. While wind speed cannot completely remove the spread of the virus, ventilation helps remove aerosols that carry the virus to reduce airborne transmission. For example, studies using simulations to track infected aerosol plumes in real time have found that a stable state of the atmosphere with low wind speeds, low-level turbulence, and cool, moist ground conditions facilitates the spread of disease. The trajectory model found that the virus can travel in the air for up to 30 min, covering a radius of 200 m at a time, 1–2 km away from the original source [138]. A study used computational fluid dynamics to simulate viral air flow in an office while investigating the effects of different ventilation strategies on viral transmission. The results showed that the ventilation strategy of single ventilation had the highest infection probability [139]. Another study found that ambient winds (wind velocities range from 0 to 16 km/h) increase the complexity of secondary flows. Even at 3.05 m, the droplets flow well along the air stream and deposit on the human body and head area. Due to wind convection, the remaining droplets can travel above 3.05 m in the air, posing a potential health risk to people nearby [140]. The study also found that a reduction in ventilation rates or room capacity per person, or an increase in the ratio of infected people to susceptible people, would increase the distance of transmission. Effective environmental prevention strategies for respiratory infections require an appropriate increase in ventilation rates while maintaining sufficiently low occupancy rates [141]. Therefore, different ventilation strategies must be developed according to the actual indoor conditions to reduce the transmission of viruses in the air.

Environmental pollution factors

Particulate matter

The relationship between air pollution and COVID-19 is well-established. Further research has found that air pollution can modify host susceptibility to infection and modify the severity of disease [142]. Table 2 summarizes some key in vivo studies of air pollution on COVID-19 related targets, immune cells, and oxidative stress. PM is the main component of air pollutants. Many studies have demonstrated that PM can increase the expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine type 2 (TMPRSS2). SARS-CoV-2 can use ACE2 as an entry receptor and TMPRSS2 to activate S protein [143]. Cell studies have shown that ACE2 expression has become a risk factor for the development of COVID-19 [144]. Another study found that the expression of ACE2 and TMPRSS2 increased the infection rate of SARS-CoV-2 [145]. Therefore, PM can increase the expression of ACE2 and TMPRSS2 and affect the severity and incidence of COVID-19.

Severe COVID-19 is associated with high inflammation and elevated levels of inflammatory cytokines. Exposure to air pollutants increases the number of pro-inflammatory cytokines and immune cells that infiltrate the lungs, leading to systemic inflammation and immune disorders that reduce resistance to viruses (Fig. 2). Even low doses of PM2.5 induce lung inflammation, oxidative stress, and worsening lung impedance and histology in mice [153]. Once pathogens establish themselves, inflammation of respiratory mucous membranes caused by exposure to air pollution may lead to a higher risk of severe COVID-19 outcomes through compound inflammation [155]. For example, studies in mouse models exposed to PM2.5 have found that PM2.5 may increase IL-1β secretion through the TLR4/MyD88 and NLRP3 inflammasome pathways, leading to airway inflammation in mice [149]. Intranasal transfer of pulmonary microbiota in PM2.5 exposed mice has been found to influence PM2.5 induced lung inflammation and oxidative stress, such as increased levels of pro-inflammatory cytokines and dysregulation of biomarkers associated with oxidative damage [154]. PM exposure may promote the development of cytokine storms in SARS-CoV-2 infection.

PM2.5 not only damages the lungs directly exposed to air, but also causes pathological changes in other organ systems through excessive oxidative stress generated by

Table 2 Mechanism research link air pollution to COVID-19

Model	Air pollutant dosage	Target	Effect	Reference
PM combined with BLM induced lung fibrosis mice (intratracheal administration)	200 μg/20 g	ACE2 and TMPRSS2	PM administration alone elevated the expression of ACE2 but not significantly; PM administration remarkably enhanced ACE2 and TMPRSS2 expression when combined with bleomycin treatment	[146]
PM- treated mice (intratracheal instillation)	50 μl (500 μg/body)	ACE2 and TMPRSS2	PM-exposed lung tissues showed increased ACE2 and TMPRSS2 expression in the alveolar regions	[147]
PM1-treated rats	whole-body expose (3 and 6 months)	ACE2, AT1, and AT2	ACE2 had increased at 3 months and was significantly decreased at 6 months; smooth muscle hypertrophy had occurred after 6 months; AT1 and AT2 had significantly decreased at 6 months	[148]
PM2.5-treated mice (intratracheal instillation)	50 μl (0.5 mg)	IL-1β, TLR4/MyD88 pathway, and NLRP3 inflammasome	Induced acute lung inflammation by PM2.5 exposure; ↑neutrophils, lymphocytes and macrophages; ↑TLR4, MyD88, NF-κB, NLRP3, P2X7 mRNA levels of lung tissues	[149]
PM2.5-treated mice (oral-nasal exposure system)	750 μg/m^3 (4h/6 weeks)	TNF-α, IL-1β, IL-18, HMGB1, NLRP3, ASC, and Caspase-1	↑TNF-α, IL-1β, and IL-18 levels; ↑mRNA expression levels of HMGB1, NLRP3, ASC, and Caspase-1 significantly	[150]
PM2.5- treated NC or HFC Apo $E^{-/-}$ mice	235.76 ± 72.73 μg/m^3 (8h/16 weeks)	TNF-α, NLRP3, ASC, caspase-1, IL-1β, and IL-18	Activated of NLRP3 inflammasome; ↓IL-10; ↑TNF-α, protein expression of NLRP3, ASC, caspase-1, IL-1β, and IL-18	[151]
Exposure to PM2.5 in atmosphere and ambient aerosol-mice (C57BL/6, $Nox2^{-/-}$ C57BL/6, Balb/c, Tlr4Lps-d (BALB/cAnPt), c-fmsYFP (FVB/N)	Facility (10.7 ± 2.1 μg/m^3) and chamber (92.4 ± 2.1 μg/m^3); 6 h/day 5 days/week	NADPH, TLR-dependent gene expression,	PM2.5 increases inflammatory monocytes via TLR4 pathway; increase NADPH oxidase–derived superoxide; influence leukocyte trafficking in the microvasculature; ↑TLR-dependent gene expression; ↑TNFα, MCP-1, and IL12p70 in lung; ↓IL-10	[152]
PM2.5-treated BALB/c mice (intranasal instillation)	PM2.5 from Sao Paulo, Brazil (10 μL or 30μL)	IL-6 and TNF-α	PM2.5 increases elastic and viscoelastic components of lung mechanics; ↑MPO, IL-6, CAT, and TNF-α; neutrophil influx into lung parenchyma; ↓GSH/GSSG	[153]
PM2.5-treated ICR mice	3 days (25mg/kg)	Lung microbiota	↑TNF-α and IL-1β in BALF; ↓GSH, mt-Nd5, and mt-Nd6; ↑NPTX1, NLRP3; disrupted microbiota can influence inflammation and oxidative stress	[154]

Abbreviations: PM particulate matter, *BLM* bleomycin, *AT1* angiotensin II receptor type, *AT2* 2, *Ozone* O3, *IL-1β* Interleukin-1 beta, *TLR4* Toll-like receptor 4, *MyD88* Myeloid differentiation primary response protein MyD88, *NLRP3* LRR and PYD domains-containing protein 3, *P2X7* P2X purinoceptor 7, *IL-18* Interleukin-18, *HMBG1* High mobility group protein B1, *Apo* $E^{-/-}$ apolipoprotein $E^{-/-}$, *ROS* reactive oxygen species, *Nrf2* nuclear factor erythroid 2-related factor 2, *TLR* toll-like receptor

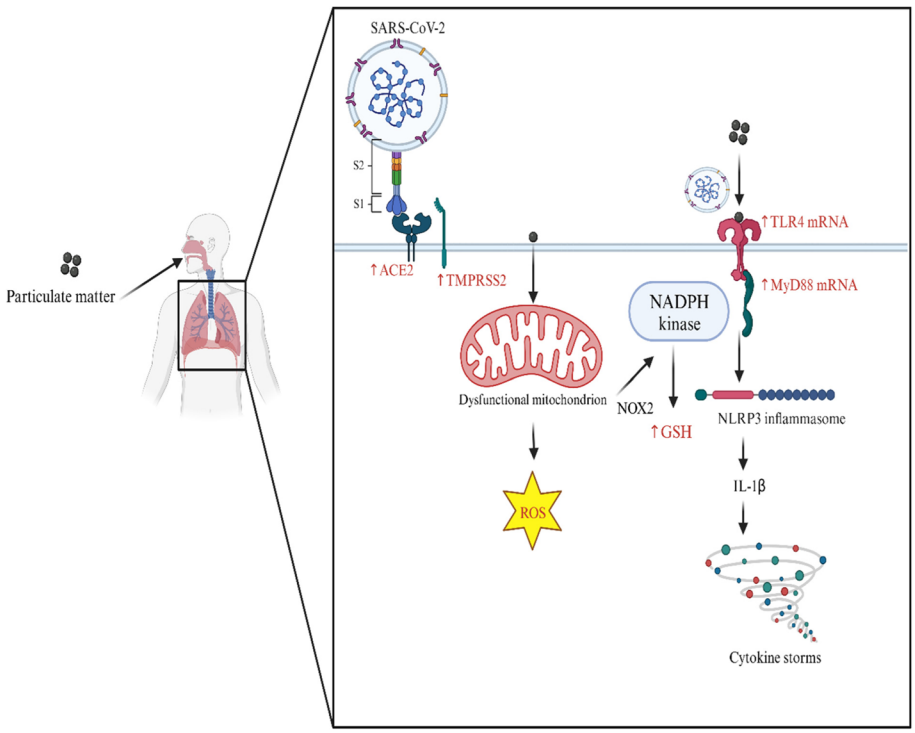

Fig. 2 Schematic diagram of the influence of particulate matter on the transmission of COVID-19. Promote (up arrow, color red) related mechanisms

mitochondria [156]. Inflammation, oxidative stress, and cell death in alveolar epithelial cells caused increased mitochondrial division and decreased mitochondrial fusion when exposed to PM2.5 [157]. The enzymes NOX2 (produce reactive oxygen species) and Toll-like receptor 4 (TLR), have been shown to be critical for PM-induced NADPH oxidase activation. PM2.5 triggers an increase in phospholipid oxidation in the lungs, which then mediates systemic cellular inflammation through TLR4/NADPH oxidation-dependent mechanisms [152]. In the case of influenza A virus infection, activation of NOX2 oxidase can promote the production of reactive oxygen species to inhibit antiviral and humoral signaling networks [158]. Therefore, PM can increase the infection rate of SARS-CoV-2 by activating NOX2 to promote reactive oxygen species. Contaminant-induced oxidative stress and cell damage may worsen prognosis [159, 160]. Exposure to air pollution-induced oxidative stress is a key mechanism leading to cardiovascular morbidity and mortality [161].

Ozone

Ozone is also a common air pollution in cities. It is a gaseous component that is produced by the interaction of air pollution components such as nitrogen oxides and organic compounds caused by sunlight. Inhaling ozone is very toxic to the lungs. Table 3 summarizes the mechanisms by which ozone may be associated with COVID-19. After inhalation, ozone does not enter cells, but comes into direct contact with the first layer of cells on the surface of the airway, such as airway and alveolar epithelial cells and airway macrophages [162]. These cells release reactive oxygen species and various other inflammatory mediators, including cytokines and lipids, from oxidative damage to the airway epithelium [163]. Oxidative stress is a major pathogenic factor of COVID-19. For example, it has been found that ozone stimulated macrophages to secrete pro-inflammatory cytokines (IL-1α, IL-1β and IL-18), and IL-1α stimulated epithelial cells to secrete CXCL1 and CCL2, thereby driving neutrophil influx [164]. Another study found that canonical transient receptor potential 6 (TRPC6) regulates NF-κB activation and intercellular adhesion molecule-1 (ICAM-1) expression after exposure to ozone. TRPC6 deficiency attenuates O3-induced recruitment of neutrophils to airway epithelial cells and ICAM-1 expression [165]. In addition, ozone can lead to loss of antioxidant Nrf2 and SOD activity in the body, enhanced intracellular oxidative stress and increased HIF-1α signaling, resulting in a persistent chronic inflammatory environment in the lungs [166]. Ozone can induce the expression of MAPK, NF-κB and AP-1 proteins through TLR4/MyD88 pathway, resulting in inflammatory response. Heat shock protein 70

Table 3 Mechanism research link ozone to COVID-19

Model	Air pollutant dosage	Target	Effect	Reference
O3-treated OVA induced asthma mice	3 ppm mixed with air for 3 h (expose one hour)	ROS	O3 exposure increased ROS release and asthma exacerbation and elevated neutrophil lung infiltration; O3 increased pro-inflammatory cytokine production as well as the percentage of IL-17A γδT cells	[170]
O3-treated rat alveolar macrophage cell line NR8383; NR8383-conditioned media- treated alveolar type I–like cells	100, 200, and 400 ppb for 1 h 24 h in media	IL-1α, IL-1β, CXCL1, CCL2	↑IL-1α, IL-1β, IL-2, GM-CSF, and IL-18in supernatant of NR8383 cells exposed to 100 ppb ozone; ↑CINC-1 and MCP-1 in supernatants from the epithelial cells;	[164]
O3-treated wild-type, TRPC6$^{-/-}$, and TRPC6$^{-/+}$ C57BL/6 mice; human airway epithelial cell ((human airway epithelial cell)	1 ppm for 3 h/day with repeated exposure every other day (days 1, 3, and 5)	TRPC6	O3-induced neutrophil recruitment to airway epithelial cells; ↑ICAM-1; TRPC6-dependent Ca^{2+} entry ICAM-1-mediated O3-induced neutrophil adhesion to airway epithelial cells	[165]
O3-treated C57BL/6 mice	3 ppm for 3 h/day, 2/week (1, 3 or 6 weeks)	HDAC2, Nrf2, and HIF-1α	Induce lung injury; increase inflammatory cell number; ↑KC, IFN-γ, MIF, TNF-α, IL-6, and IL-17; ↑SOD, HIF-1α, Nrf2, Gpx1 mRNA, Txnrd1 mRNA, pHDAC2; ↓HDAC2	[166]
O3-treated C3H/HeJ (HeJ; Tlr4 mutant) and C3H/HeOuJ (OuJ; Tlr4 normal) mice	0.3 ppm for 6, 24, 48, or 72 h	TLR4	↑p65, AP-1; ↑transcript levels of Myd88 and Trif; ↑ERK1/2 and p38;	[167]
O3-treated human (13 healthy, 4 allergic non asthmatics, 10 allergic asthmatics)	0.4 ppm for 2 h	IL-1β and IL-8	Post exposure, show activated innate immune function; ↑IL-1β and IL-8;	[171]
O3-treated OVA-established asthmatic mouse model	1 ppm for 3 h/day/3 times	ROS	Enhance AHR and decrease CL; increase the number of total leukocytes, macrophages, neutrophils; ↑HA, IFN-γ, CXCL-1, TNF-α, and IL-17; ↑phosphorylation level of p38 MAPK and HSP27; ↑MDA, GSH-Px;	[172]

Abbreviations: h hour, *CXCL1* cytokine-induced neutrophil chemattractant-1, *CCL2* monocyte chemoattractant protein-1, *TRPC6* canonical transient receptor potential 6, *ICAM-1* intercellular adhesion molecule-1, *Gpx1* glutathione peroxidase 1, *HDAC2* histone deacetylase 2, *Nrf2* nuclear factor erythroid-related factor 2, *HIF-1α* hypoxia-inducible factor-1α, *ERK1/2* extracellular-signal–related kinase-1/2, *AP-1* activator protein-1, *AHR* airway hyperresponsiveness, *CL* lung compliance, *HA* hyaluronan

(HSP70) was identified as a downstream mediator with ozone mediated TLR4 effects [167]. Ozone also induced apoptosis markers (lysed caspase 9) and autophagy markers (beclin-1) in alveolar macrophages and enhanced the expression of MMP-2 and MMP-9 [168]. However, the effects of ozone on different cell death pathways such as necrosis, apoptosis, ferroptosis, and autophagy have not been resolved [169]. These cell death pathways may be responsible for the emphysema process induced by oxidants. Just as ozone can make asthma worse, ozone may increase the incidence and severity of COVID-19 by inducing inflammation, oxidative stress, and airway remodeling (Fig. 3).

Ozone is an excellent biocidal agent due to its strong oxidation, and its effectiveness against bacteria, fungi and viruses has been proven [173]. Ozone can be easily applied to large and small areas for disinfection and is broken down back into safe oxygen after treatment. Ozone is particularly deadly to viruses through peroxidation of lipid surface and subsequent damage to lipid envelopes and proteins, and enveloped viruses such as SARS-CoV-2 are more vulnerable to ozone attack [174]. Ozone has been shown to inactivate the SARS-CoV-2 virus on surfaces (such as plastic, glass, stainless steel, gauze, wood, wool, copper, and coupons in ambulance seats and floors) or in suspended fluids [175]. During the pandemic, ozone has been widely used to purify many enclosed spaces.

Ozone also has medical uses. Medical ozone is administered in the form of a balanced O2/O3 mixture by autologous blood therapy or rectal blow or also as a peritoneal injection in laboratory animals [176]. Medical ozone can interfere with the replication phase of the virus to play an antiviral role. Medical ozone's effects include the oxidation and inactivation of specific viral receptors used to form cell-membrane binding structures, thereby inhibiting the level of its first stage: cellular penetration [177]. Medical ozone can directly act on Nrf2, an important nuclear message transmitter, regulating and blocking the activity of ACE2 receptors. Thus, preventing SARS-CoV-2 from replicating [178]. SARS-CoV2 can cause oxidative stress and inflammation, further tissue damage and widespread triggering of the clotting cascade, culminating in the formation of blood clots [179]. Medical ozone, when administered in appropriate pathways and at small doses, may induce adaptive responses that reduce endogenous oxidative stress [180]. In addition, some studies have found that ozone can activate the cellular and humoral immune system and can reduce inflammation/apoptosis processes [177]. Clinical studies have further confirmed that ozone therapy can be used as a comprehensive treatment for COVID-19 with low cost and improve the health status of patients [181].

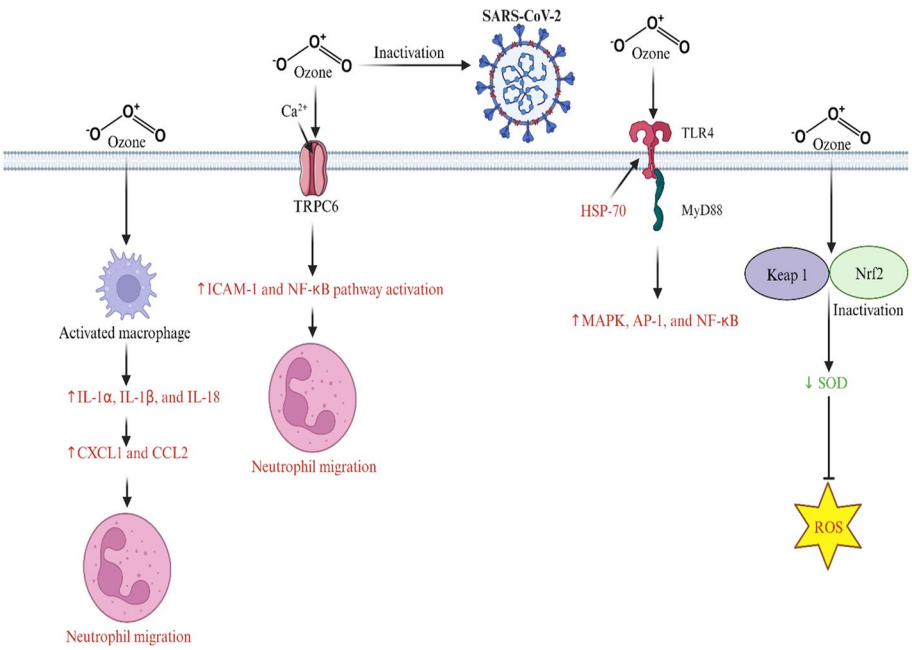

Fig. 3 Schematic diagram of the influence of ozone on the transmission of COVID-19. Promote (up arrow, color red) or suppressing (downward arrow, color green) related mechanisms

Discussion

Since the outbreak, extensive research has investigated the factors that influence the spread of COVID-19. Representative studies on the impact of natural environmental factors and social environmental factors on COVID-19 are discussed in this review. The mechanisms and results of natural environmental factors affecting COVID-19 are shown in Fig. 4. As can be seen from the epidemiological studies included in this paper, the current study covered multiple regions, multiple confounding factors, and long or short-term exposure times. The mechanism study also covers multiple pathways and targets in vivo and in vitro.

Both mechanism and epidemiological studies have shown that air pollution, especially PM2.5 and ozone, greatly accelerates the spread of COVID-19. Some of the differences in air pollution effectiveness in transmitting the virus may be caused by differences in composition between different locations. However, there are important limitations to the available evidence, such as (1) methodological limitations, (2) incomplete coverage of the original data, and (3) large uncertainties in the analysis [182, 183]. Studies on the mechanism of air pollution affecting the spread of COVID-19 have confirmed that air pollution can (1) increase the expression of key proteins in the entry pathway of SARS-CoV-2, (2) promote inflammation and release of pro-inflammatory cytokines, (3) causes pathological changes in organ systems, and (4) increase the risk of respiratory complications. This further provides evidence for COVID-19 prevention and control measures to reduce air pollution, rational use of ozone disinfection, and medical ozone therapy. To date, no study has accurately demonstrated seasonal changes in the global prevalence of COVID-19. Research on climate conditions is subject to similar challenges and limitations as air pollution [184]. But a growing body of evidence supports a statistically significant correlation between climatic conditions and morbidity, mortality, recovery cases, etc. [185]. In vitro experiments were conducted to study the activity of the virus under different climatic conditions and substrate conditions. Studies have shown that the SARS-CoV-2 has the longest half-life

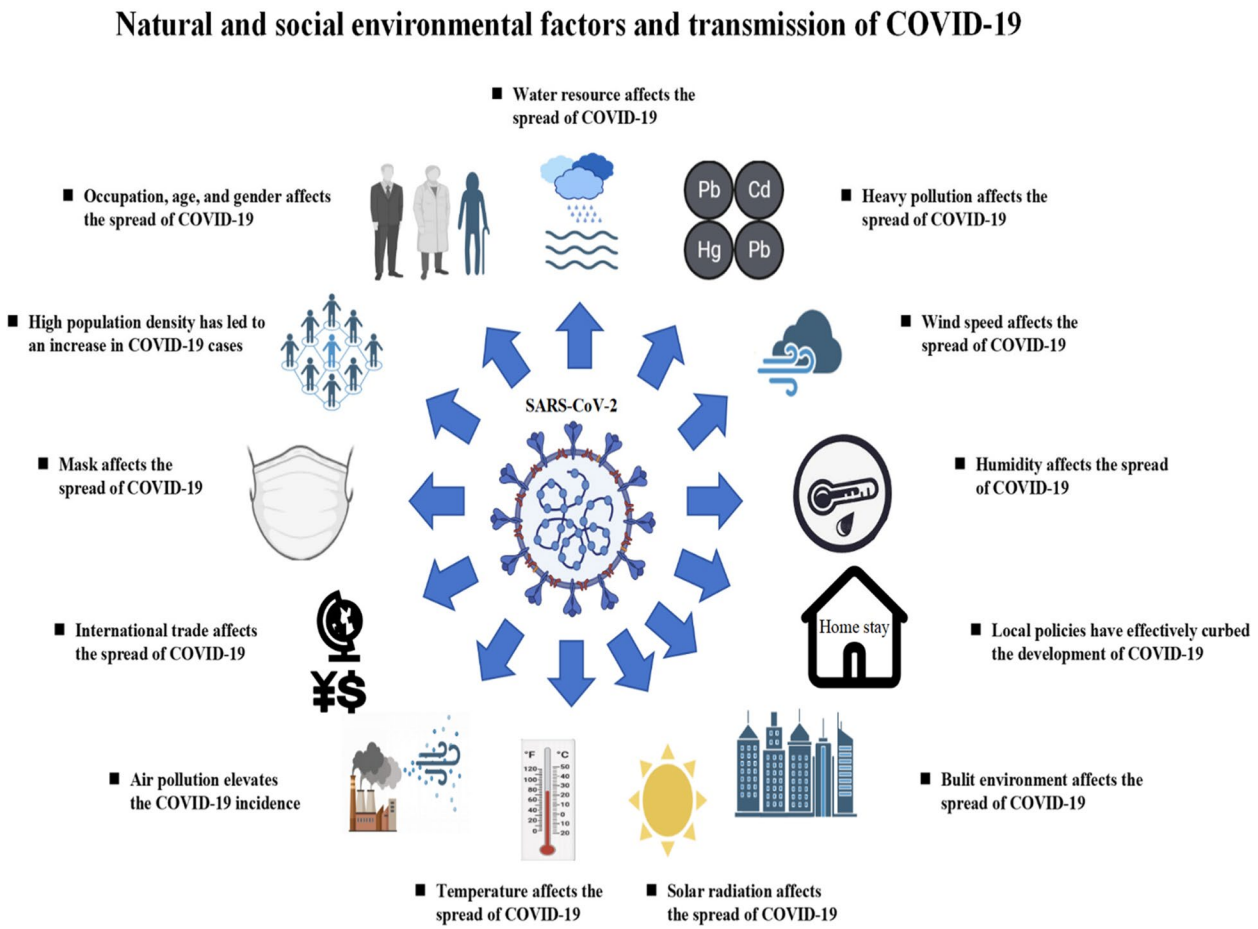

Fig. 4 Schematic diagram of nature and social environment factors affects the transmission of COVID-19

at lower temperatures, which promotes SARS-CoV-2 transmission. This also provides evidence for COVID-19 prevention and control measures to maintain indoor temperature and humidity. SARS-CoV-2 rots faster at higher relative humidity, inhibiting the spread of the virus. Solar radiation has a better inactivation effect on SARS-CoV-2, but UVC in the environment cannot directly eradicate SARS-CoV-2. Solar radiation (UVB) inhibits the spread and development of COVID-19 through the synthesis of vitamin D. Therefore, there is scientific evidence for COVID-19 prevention and control measures based on rational exposure to sunlight. For other climatic conditions (such as wind speed, water resource), no clear conclusions have been found.

Social environmental factors are also significantly related to the spread of COVID-19. The mechanisms and results of social environmental factors affecting COVID-19 are shown in Fig. 4. People vary greatly in their daily routines, traveling from home, work, school, and public and commercial spaces can exhibit high personal exposure to pathogens [186]. Epidemiologic studies have shown that population density, built environment, occupation, age, gender, local policies and socioeconomic activity have an impact on COVID-19 [187]. This is also the scientific basis for the country to take measures such as control of population movement, control of population density, wearing masks, and disinfecting dense places [188]. Among them, population density is considered to have a more significant impact on COVID-19 than meteorological factors, and the increase in population density will in turn lead to an increase in COVID-19 cases and deaths [73]. In addition, socio-economic activities such as international trade are also key factors affecting the spread of COVID-19. The total import and export volume is highly positively correlated with confirmed cases [97]. Although there are differences between the results of the studies, this may be due to the limitations of the studies introducing bias. Like the limitations described earlier, single factor studies can be biased due to confounding factors at the individual level.

Future prospects

Now, as vaccination coverage increases and strains mutate, COVID-19 may be transitioning to an epidemic seasonal disease, such as influenza [189]. Climate may play a bigger role in determining COVID-19 infection. In the near term, as public health measures are reduced, the link between COVID-19 and natural environmental factors will become clearer. Future studies are needed to determine the effects of climate change on the spatiotemporal distribution of different strains of viruses. In addition, future research could focus on disease outcomes caused by climatic conditions in animal models of COVID-19, and further improve the range of environmental conditions used in laboratory studies to better simulate real-world environmental conditions (indoor and outdoor). A meta-analysis of climate-related epidemiologic should be attempted to provide more conclusive evidence.

In addition, it is worth studying whether long-term environmental changes and short-term climate changes have the same effect on the human body. The impact of environmental exposure changes throughout life [190]. We do not know how the duration of exposure will affect the susceptibility and severity of COVID-19. Existing mechanism research is focused on animal experiments, and ethical clinical trials are needed. Existing mechanism studies have found that both temperature and humidity, as well as air pollution, can have an impact on immunity. Future research should address the interaction between climate and immunity. Explore the specific mechanism of climate on immunity through clinical research.

Conclusions

The impact of COVID-19 on human health is significantly negative. The constant change of the current environment increases the probability of infectious diseases. Sorting out the key factors affecting infectious diseases for scientific prevention and control, personalized and precise treatment is critical, although there is still a lot of work to be done. Our review indicates that with the continuous mutation of SARS-CoV-2, high temperature, high humidity, low air pollution levels, and low population density may be more likely to slow down the spread of the virus. All of these measures appear to be effective in controlling the spread or mortality of COVID-19: (1) reducing air pollution levels, (2) rational use of ozone disinfection and medical ozone therapy, (3) rational exposure to sunlight, (4) scientific ventilation and maintenance of indoor temperature and humidity, (5) control of population density, and (6) control of population movement. They could play a vital role in the future face of infectious diseases. The arrival of new pathogens is inevitable. While focusing on the research and development of vaccines, diagnostic reagents, and drugs for infectious diseases, we use interdisciplinary methods to break through existing limitations and clarify the impact of environment on biology, disease and evolution from the molecular level with the development of methodology. It is an urgent need to safeguard people's health. This will provide innovative inspiration for global epidemic prevention and control policies and provide reference for similar infectious diseases that may emerge in the future.

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Authors' contributions
Conceptualization: Yanping Wang, Bin Liu, and Nannan Shi; original draft preparation, Zhaoyuan Gong, Tian Song, and Mingzhi Hu; writing-review & editing, Qianzi Che, Jing Guo; and project administration, Haili Zhang and Huizhen Li. All authors read and approved the final manuscript.

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Availability of data and materials
Not applicable.

Data availability
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Declarations

Ethics approval and consent to participate
Not applicable.

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Competing interests
The authors declare no competing interests.

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