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High altitude Relieves transmission risks of COVID-19 through meteorological and environmental factors: Evidence from China

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ABSTRACT

Existing studies reported higher altitudes reduce the COVID-19 infection rate in the United States, Colombia, and Peru. However, the underlying reasons for this phenomenon remain unclear. In this study, regression analysis and mediating effect model were used in a combination to explore the altitudes relation with the pattern of transmission under their correlation factors. The preliminary linear regression analysis indicated a negative correlation between altitudes and COVID-19 infection in China. In contrast to environmental factors from low-altitude regions (<1500 m), high-altitude regions (>1500 m) exhibited lower PM2.5, average temperature (AT), and mobility, accompanied by high SO2 and absolute humidity (AH). Non-linear regression analysis further revealed that COVID-19 confirmed cases had a positive correlation with mobility, AH, and AT, whereas negatively correlated with SO2, CO, and DTR. Subsequent mediating effect model with altitude-correlated factors, such as mobility, AT, AH, DTR and SO2, suffice to discriminate the COVID-19 infection rate between low- and high-altitude regions. The mentioned evidence advance our understanding of the altitude-mediated COVID-19 transmission mechanism.

1. Introduction

The outbreak of novel respiratory disease 2019 (COVID-19) has posed a global health crisis (Cao, 2020). With the rage of COVID-19, there have been over 0.24 billion confirmed cases and 4.99 million deaths as of 30 October 2021 according to John Hopkins University (Hopkins, 2021). COVID-19 infects host cells via binding their trans-membrane protein ACE2 (angiotensin-converting enzyme 2), together with transmembrane serine protease 2 (TMPRSS2) (Li et al., 2020). The typical clinic symptoms of COVID-19 infected patients were cough, fever, dyspnea, myalgias, diarrhea, nausea, and vomiting (Goyal et al., 2020), with a low incidence of congestion, rhinorrhea, sore throat and diarrhea (Fu et al., 2020). Understanding the environmental indicator of COVID-19 contributes to guiding public health policy-making. Imposed city lockdown, and quarantine measures sharply reduced newly confirmed cases (Lian et al., 2021). Though population flow drives spatio-temporal distribution of COVID-19 in China (Jia et al., 2020), available epidemiological data from Americas implied a correlation between altitudes and the incidence of COVID-19, such as Argentina, Brazil, Canada, Colombia, Costa Rica, Ecuador, Mexico, Peru, and USA (Arias-Reyes et al., 2020a; Millet et al., 2021; Segovia-Juarez et al., 2020). For instance, the average COVID-19 infection rate in the United States decreased by 12% per 495 m of elevation (Stephens et al., 2021). The relative mechanism for this phenomenon remains unclear.

High-altitude regions (e.g., Tibetan region of China) exhibited lower COVID-19 prevalence due to the relatively low population and mobility (Arias-Reyes et al., 2020a). Adjusted regression models including population density supported a negative correlation between COVID-19 cases and altitudes (Cano-Pérez et al., 2020). In addition, subsequent population-scale regression analysis from the United States revealed that...
high altitudes are adverse to the transmission of COVID-19 (Stephens et al., 2021). Even though the effect of population density decreased, a noticeable difference of COVID-19 infection in high- and low-altitude regions was observed (Segovia-Juarez et al., 2020). Such divergence may decrease the half-life and survival of the virus in high UV exposure (Arias-Reyes et al., 2020a; Cadnum et al., 2020). Low pressure in high-altitude regions also affected lung physiology (Breezevoort et al., 2020). Clinic symptoms from low- and high-altitude COVID-19 patients are primarily consistent while less prone to diarrhea at high-altitude COVID-19 patients in Gansu Province (Tue et al., 2020).

The main transmission route of COVID-19 includes direct contact, respiratory droplet, and fecal-oral route (Hindson, 2020). Extensive studies have explored the role of social parameters (e.g., migration scale index and population density), climate factors (e.g., temperature, humidity, rainfall) and air pollutants (NO\(_2\), SO\(_2\), CO) in COVID-19 transmission (Jia et al., 2020; Tian et al., 2021; Shakil et al., 2020; Zang et al., 2022). For instance, the Ensemble Empirical Mode Decomposition (EEMD) analysis indicated the limited seasonal modulations on COVID-19 evolution (Huang et al., 2021). It has also been reported that high altitudes can influence the occurrence and intensity of influenza A (H1N1, H5N1, H5N8) (da Costa et al., 2018; Scolamacchia et al., 2021), and decrease COVID-19 infection (Segovia-Juarez et al., 2020; Stephens et al., 2021). The high altitude at 4500 m down-regulates the expression of ACE2, thereby probably protecting them against COVID-19 replication in host cells (Mendes et al., 2019). However, the synergy effect of different factors on COVID-19 transmission needs deep inquiry.

Geographical distribution of China covers complete data of COVID-19 confirmed cases ranging from low- and high-altitude regions, it can be adopted as a model to explore the relevant mechanisms of altitude-dependent COVID-19 infection. In this study, pandemic data (COVID-19 confirmed cases, death cases, as well as relevant climate factors and air pollutants) of 339 cities in China were collected. We formulated the statistical null hypotheses for falsification: H1\(_0\) there are no inverse correlations for altitude with COVID-19 confirmed cases; H2\(_0\) altitude has no effect on environmental factors (CO, NO\(_2\), PM2.5, PM10, SO\(_2\), O\(_3\), AT, AH, DTR and mobility); H3\(_0\) environmental factors (CO, NO\(_2\), PM2.5, PM10, SO\(_2\), O\(_3\), AT, AH, DTR and mobility) have no effect on COVID-19 confirmed cases.

To further understand explore the altitude-mediated COVID-19 transmission mechanism, an altitude-infection rate nonlinear regression analysis validated the hypothesis that high altitudes reduce COVID-19 infection. A comparative analysis of environmental factors were conducted in low-altitude regions (<1500 m) and high-altitude regions (>1500 m). Utilizing nonlinear regression analysis explored the relationship between altitude-related factors and COVID-19 infection. Subsequently, the multiple mediating effect model analysis elucidated the mechanism of altitude-mediated COVID-19 infection. The mentioned findings provide profound insights into the relationship between altitudes and COVID-19 infection in China.

2. Material and methods

2.1. Collection of COVID-19 confirmed cases

A dataset of daily confirmed cases of COVID-19 was collected from 10 January 2020 to 10 May 2021 by excluding the imported cases in China. Data collection can fall to two time periods: (i) During January 10 to March 1, which involved average temperature (AT), diurnal temperature range (DTR), absolute humidity (AH) and air pollutants (e.g., PM2.5, PM10, SO\(_2\), CO, NO\(_2\), and O\(_3\)). All altitude data for 74 cities originated from the National Geomatics Center of China (NGCC, 2021). Mobility for 74 cities from Jan 10 to March 1 was determined according to Baidu Migration Map (Qianxi, 2021).

The R package of nCOV 2019 (Wu et al., 2020) was adopted to summarize the daily cumulative chart of confirmed cases by provinces and cities in China as of March 1. The infection summary map was employed in ArcGIS 10.7.

2.2. Environmental factors collection

High-altitude region was above 2500 m (Moore and Regensteiner, 1983). Given the topography of China, the altitude falls to typical three terrain grades, which covers Qinghai-Tibet Plateau (Grade I > 4000 m above sea level), major basin regions of China (Grade II with an altitude of 1000–2000 m), and main plains of China (Grade III < 500 m above sea level). In contrast to Grade III, the altitude variations in Grade I and II revealed distinct environmental factors. Based on the confirmed COVID-19 patients in China, high-altitude regions (>1500 m) and low-altitude regions (<1500 m) represent below 1500 m and above 1500 m, respectively.

To examine the correlation between environmental factors and COVID-19 infection in-depth, various meteorological data, air pollution and urban basic data from 74 cities were collected, respectively (Table S1). Meteorological data were obtained from the information center of ministry of ecology and environment of the People’s Republic of China (CMA, 2021) from January 10 to March 1, which involved average temperature (AT), diurnal temperature range (DTR), absolute humidity (AH) and air pollutants (e.g., PM2.5, PM10, SO\(_2\), CO, NO\(_2\), O\(_3\)).

To explore the altitude-mediated COVID-19 transmission mechanism, we employed the statistical null hypotheses for falsification:

H1\(_0\): There are no inverse correlations for altitude with COVID-19 confirmed cases.

H2\(_0\): Altitude has no effect on environmental factors (CO, NO\(_2\), PM2.5, PM10, SO\(_2\), O\(_3\), AT, AH, DTR and mobility).

H3\(_0\): Environmental factors (CO, NO\(_2\), PM2.5, PM10, SO\(_2\), O\(_3\), AH, DTR and mobility) have no effect on COVID-19 confirmed cases.

To test H1\(_0\) hypothesis, we applied linear regression (F-test) to understand the relationship between confirmed cases of COVID-19 and altitudes from 74 cities. Taking into consideration of strict city lockdown measures, relevant data of Hubei Province were excluded. To test H2\(_0\) hypothesis, we provided a comparative analysis of environmental factors at low- and high-altitude regions by two independent t-test using SPSS v.20.0. The results were expressed as mean ± SEM. p-value of <0.05 was considered statistically significant. Subsequently, spearman correlation analysis (F-test) was applied to examine the correlation between environmental factors and altitude.

To test H3\(_0\) hypothesis, a nonlinear regression (F-test) model was exploited to explore the correlation between confirmed cases and various factors (AH, AT, DTR, PM2.5, PM10, SO\(_2\), CO, NO\(_2\), and O\(_3\), and mobility), respectively. We calculated correlation coefficients to test the hypotheses and to assess the strength of relationships.

All nonlinear curve fit complied with spearman correlation by applying RStudio 4.0.3. A significant difference of nonlinear regression analysis was identified at p < 0.05.

Finally, we created a mediation model analysis to test the H4\(_0\) hypothesis. To further explore whether altitude-mediated COVID-19 infection, a mediation model was used to evaluate the association between altitude and confirmed cases mediated by environmental factors.
If the 95% CI of indirect effect did not contain 0, it indicated that the mediating effect was significant. The mediation model was controlled for covariates (CO, NO₂, PM2.5, PM10, SO₂, O₃, AT, AH, DTR and mobility) and the study variables were standardized. If there is an intermediary variable, it indicates the existence of the mediation effect (Liang et al., 2021). Such a nonparametric technique has been extensively adopted to analyze small sample sizes since it can effectively avoid the interference of original data distribution. The detailed procedures of mediating effect are described as previously (Rucker et al., 2011; Zhu et al., 2020c).

All regression analyses have been carried out using the statistical package R version 3.5.

3. Results

3.1. High altitude decreases on COVID-19 confirmed cases

To reflect the correlation between COVID-19 confirmed cases and altitudes the basic statistics information from 8178 confirmed cases covering 74 cities of China were collected from January 2020 to May 2021 (Fig. 1a). The confirmed cases of COVID-19 exhibited obvious aggregation and distribution nearby Hubei Province. Several contiguous provinces (Hunan, Henan and Anhui) had higher COVID-19 confirmed cases ranging from 1000 to 10,000. In contrast, other contiguous provinces, including Jiangxi, Chongqing, Shanxi, attenuated the confirmed cases of COVID-19. Subsequent linear regression analysis (R = 0.415) showed a significant negative correlation between altitudes and COVID-19 confirmed cases (Fig. 1b), which challenged the H₁₀ hypothesis. COVID-19 data from Argentina also shared a similar trend with that of China (Fig. 1c). These evidence indicate altitude-dependent COVID-19 infection may be a universal phenomenon.

3.2. Comparative analysis of environmental factors at low-and high-altitude regions

Previous analysis revealed that altitudes reduced the COVID-19 infection in China, we speculated that environmental factors in high-altitude regions are responsible for the COVID-19 infection. High-altitude regions significantly decreased PM2.5, AT, AH and mobility (p < 0.05), along with high level of SO₂ and DTR as compared to the low-altitude regions, (Fig. 2). The change in altitudes has no significant impact on the PM10, CO, O₃, and NO₂ (p > 0.05). Among all parameters, air pollutants SO₂ at >1500 m was 2-fold higher than at <1500 m (Fig. 2c). Climatic factors (e.g., AT and AH) are sensitive to altitude changes; their levels above 1500 m were 5.1- and 3.8-fold lower than that below 1500 m, respectively (Fig. 2g, 2i). Although imposed quarantine measures in high-altitude regions showed less than 50% mobility of low-altitude regions (Fig. 2j). Spearman correlation analysis was carried out to examine the correlation between environmental factors and altitude (Table 1). Notably, PM2.5, PM10, SO₂, CO, and DTR were positively correlated with altitudes with an r-value of >0.24, while altitudes were negatively correlated with mobility, AT and AH, and their correlation coefficients were −0.236, −0.460, and −0.497, respectively. However, there was no significant correlation between altitudes, NO₂ and O₃. Collectively, this findings disproved H₂₀ hypothesis, namely, altitude has a significant correlation with environmental factors except for NO₂ and O₃.

Fig. 1. a, Geographic patterns of COVID-19 confirmed cases from China as of May 31, 2020; b, c, Linear correlation analysis between altitudes and infection rate of COVID-19 in China (b) and Argentina (c).
3.3. **Environmental factors of the COVID-19 transmission**

To explore whether environmental factors have an effect on COVID-19 infection in China, spearman correlation analysis was applied to investigate the correlation between COVID-19 infection and environmental factors (Table S2, Fig. 3). Based on the correlation coefficients, the mentioned environmental factors are divided into three categories, namely dominant, secondary and other factors.

3.3.1. **Mobility is dominant factor for COVID-19 infection**

Mobility represents the behavior of the travelers leaving from one city to another city for short time period by spatial displacement, including airplane, high-speed rail, ship, coach and private car. It was observed that the change of mobility is positively correlated with COVID-19 infection (Fig. 3a). Mobility > 1, it slightly contributed to the increase in confirmed cases; whereas COVID-19 infection dramatically increased when the mobility exceeded 2.

3.3.2. **AT, DTR, AH, CO and SO**

An obvious S-shaped curve was observed between environment factors (AT, SO2) and COVID-19 confirmed case (Fig. 3b,3c). The level of SO2 has a negative correlation with confirmed cases above a threshold of 8 μg m−3, and then confirmed cases rebounded near 25 μg m−3. However, AT ranging from 0 to 15 °C exhibited a positive correlation with confirmed cases while AT below 0 °C showed a low distribution of COVID-19 infection (Fig. 3c). Unlike SO2, the relationship between CO and confirmed cases is an arched curve (Fig. 3f), and the cases reached the maximum level when the concentration of CO was 0.8 mg m−3. Similarly, COVID-19 confirmed cases increased first and then decreased with the changes of AH (Fig. 3d), its corresponding threshold values was 6 g m−3. As opposed to the mentioned, DTR has a negative relationship with confirmed cases, and possessed three different slopes (Fig. 3e).

Thus, we can challenge the H3 hypothesis because environmental factors (e.g. mobility, AT, DTR, AH, CO and SO2) have an impact on COVID-19 confirmed cases.

3.3.3. **O3, NO2, PM2.5 and PM10 have no impact on COVID-19 infection**

In the mentioned parameters, other factors (e.g. O3, NO2, PM2.5, and PM10) did not impact COVID-19 infection (Table S2), which was inconsistent with the existing studies (Zhu et al., 2020b). For example, 4.86 mg L−1 ozone-water could deactivate SARS in 3 min. However, the effect of altitude on PM2.5 and PM10 was significantly correlated. With the increase in altitudes, the content of particulate pollutants in the air shows an upward trend, this provides reasonable explanation of low COVID-19 infection in high-altitude regions.

3.4. **Mediation model analysis reveals altitude-mediated COVID-19 infection**

To examine the potential mechanism of altitude-mediated COVID-19 infection, a mediation model analysis was conducted to assess the correlation of altitudes, environmental factors, COVID-19 infection. As shown in Fig. 4, the environment factors of altitude on confirmed cases was negative associations (IB = −0.020, p < 0.01) and the 95% bias-corrected bootstrap confidence interval was −0.040 to 0.000, which indicated indirect effect of environment factors on confirmed cases (Table 2). In addition, the direct effect of altitude on confirmed cases (ADE = −0.020, p < 0.001) was also significant, indicating that environment factors partially mediated the relationship between altitude and confirmed cases, thereby we can disprove the H4A hypothesis (Fig. 1). These evidences suggest that the altitude can influence COVID-19 infection by changing corresponding environmental factors.

### Table 1

| Factor | correlation index(r) | P value |
|--------|----------------------|---------|
| PM2.5  | 0.244*               | 0.036   |
| PM10   | 0.291*               | 0.012   |
| SO2    | 0.475***             | <0.001  |
| CO     | 0.442***             | <0.001  |
| NO2    | 0.104                | 0.376   |
| O3     | −0.202               | 0.084   |
| Mobility| −0.236*              | 0.043   |
| AT     | −0.460***            | <0.001  |
| DTR    | 0.454***             | <0.001  |
| AH     | −0.497***            | <0.001  |

Notes: AT: ambient temperature; AH: absolute humidity; DTR: diurnal temperature range. * indicates significant difference while ns indicates no significant difference. *P < 0.05, **P < 0.01, ***P < 0.001.
4. Discussion

4.1. Altitude is negatively correlated with the COVID-19 infection

13% of the cities in China are located in middle- and high-altitude regions (>1500 m above sea level). With the improvement of infrastructure and convenient transportation, population flow at high-
altitude regions are still active. Our observations found that high altitudes is associated with the COVID-19 infection in China, in accordance with existing studies conducted in Colombia (Cano-Pérez et al., 2020), Peru (Quevedo-Ramírez et al., 2020; Segovia-Juarez et al., 2020), United States (Stephens et al., 2021), and Mexico (Woolcott and Bergman, 2020). After the effects of population density was eliminated, an obvious negative correlation between altitudes and infection rates was still identified in Peru, thereby demonstrating that altitude has the potential to influence the COVID-19 infection (Segovia-Juarez et al., 2020). However, several studies debated the pros and cons of altitude-related COVID-19 infection have been also reported previously (Luks and Swenson, 2020). Admittedly, moderate intermittent hypoxia induced by high altitude is capable of improving endogenous antioxidant capacity, mitochondrial and immune system function by inducing relevant ROS signaling, HIF and inflammatory pathways (Ivashkov, 2020; van Patot et al., 2009; Yin et al., 2007). The mentioned findings also raise the possibility of hypoxia therapy in COVID-19 patients, including steroids curing for high-altitude disease (e.g., dexamethasone), are equally effective against COVID-19, especially in patients with severe COVID-19 (Han et al., 2019).

4.2. High- and low-altitudes regions shared obvious difference in environmental factors

It is estimated that China’s urbanization rate has increased from 17% to 60.0% in 2019, with over 600 million people migrating to cities (Bai et al., 2014). Such migration with a huge population is largely located in the coastal regions (e.g., the Yangtze River Delta and the Pearl River Delta), causing high mobility in low-altitude regions. The high-altitude regions encountered a wide range of difficulties in the construction of the public transportation system, especially geological problems in the permafrost regions (Shan et al., 2014). Furthermore, the city size and population density of high-altitude regions are lower than in low-altitude regions. The mentioned limitations decreased the mobility of high-altitude regions, thereby reducing the transmission of the pandemic in high-altitude regions.

Air pollutants are composed of organic compounds, metal particles, carbon materials, and other particulate materials (even ions) (Pandey et al., 2005). Among of them, PM2.5 acts as transport medium of large amounts of toxic contaminants via adsorption (Lu et al., 2015), thus posing a health risk to human (e.g., lung disease) (Tan et al., 2017). Our studies confirmed that AT, AH and DTR affected the COVID-19 transmission of COVID-19 in Wuhan hospital (Liu et al., 2020). The stability and activity of the virus appears to be closely to AT and AH, thereby contributing to droplet mediated virus transmission (Xie and Zhu, 2020). Generally, the median half-life of the novel Coronavirus in aerosol is 2.74 h. It can live on contaminant surfaces for up to several days and still be infectious. Consequently, a combination of heat and ultraviolet light irradiation was used for the sterilization and prevention of COVID-19 (Mahanta et al., 2021). However, our studies didn’t observe a significant difference of solar radiation at low- and high-altitude regions. Thus, we believe that the solar radiation showed a negligible on the transmission of COVID-19 in China.

Unlike climatic factors, anthropogenic activities exacerbate the formation distribution of air pollutants. Our studies revealed that air pollutants (e.g. SO2 and CO) showed considerable effect on the COVID-19 infection. Once their levels reached a certain threshold, and could inhibit the transmission ability of COVID-19. Existing studies also demonstrated that 3.6 ppm of SO2 gas and 308 cm2·min−1 of simulated solar radiation kill Encephalomyelitis viral (Berendt et al., 1971, 1972). However, 150 μM CO inhibits bovine viral diarrhea virus replication in bovine to some extent (Ma et al., 2017; Zhang et al., 2017). Under normal conditions, vehicles took up 47% of total CO emissions in the air. During the Home Quarantine, CO levels in the air decreased significantly with a decline in road traffic and economic activity (Dantas et al., 2020). Nonetheless, the interactions between air pollutants and climatic factors are still underestimated.

In addition to the abovementioned factors, some other factors, e.g. vitamin D, pollens and mold spores, should not be underestimated because they are associated with complications of COVID-19. Previous studies found that vitamin D deficiency may induce acute respiratory distress syndrome (Grant et al., 2020), populations living in the high-altitude regions had less levels of vitamin D than those living at lower altitudes (Hirschler et al., 2019), along with low incidence of emphysema (Mendes et al., 2019). Thus, we speculated that low vitamin D at high-latitude regions a potential contribution to decreasing the transmission of COVID-19. In most cases, the role of pollen and mold spores in COVID-19 transmission is still controversial due to the complexity of the transmission of COVID-19 (Shah et al., 2021). It can function as potential vector of COVID-19, and could cause lung complications (Ravindra et al., 2021). However, existing studies found that pollen had a high negative correlation with the incidence of COVID-19 (Hoogeveen et al., 2021). These findings are still early speculations because it is challenging to achieve seasonal allergens exposure and lack of corresponding experimental data. Therefore, our study incorporated pollen nucleomycoses spores and other factors into PM2.5 and PM10 to
avoid the deviation caused by a single factor.

4.4. Altitude mediated COVID-19 infection by changing environmental factors

Negative binomial regression model analysis, coupled with lag model can accurately assess the correlation between environmental factors and COVID-19 infection (Zhou et al., 2021). Another study utilized meta-analysis to integrate existing COVID-19 (Gupta et al., 2020). However, these analysis underestimate the main driven factors (e.g. altitude) associated with COVID-19 infection (Bashir et al., 2020; Ma et al., 2020; Pirouz et al., 2020; Wang et al., 2020). Our studies combined the nonlinear regression analysis and mediating effect to elucidate the altitude-mediated COVID19 transmission mechanism (Fig. 4). Similarly, the altitude-driven influence of various factors on the transmissible capacity of epidemics has been found in H1N1(Perez-Padilla et al., 2013), H7N9 (Qiu et al., 2014), HIV (Hoshi et al., 2016) and other dengue (Hurtado-Díaz et al., 2007). The rational allocation of public health resources can be facilitated by studying the spatial and temporal characteristics of COVID-19 transmission, disease prevention and control of public health workers, flexible prevention and control strategies in different risk areas and effective prevention measures in high-risk areas.

Collectively, our study provided a novel insight on altitude-mediated COVID-19 infection via nonlinear regression and mediating effect model, and reported altitude-related environmental factors (e.g. SO2, CO, mobility, AT, AH and DTR) as main contributors of COVID-19 infection. Though existing studies reported a higher COVID-19 mortality rates in U.S. counties located at >2,000 m elevation versus those located <1,500 m (Woolcott and Bergman, 2020), no relationship between altitude and COVID-19 mortality rates was observed in China. Such divergence is correlated with lower confirmed patients in high-altitude region of China. It’s worth noting that low confirmed cases in high-altitude regions do not mean that low mortality, COVID-19 deaths mainly are induced by the patient’s own symptoms.

4.5. Study limitations

Due to the complexity and diversity of environmental factors, there are limitations in the research of COVID-19. In order to improve the accuracy of assumptions, a variety of different prediction models to validate altitude-mediated COVID-19 transmission could be used. On the other hand, the research on the impact of COVID-19 infection rate should be expanded, including R0, epidemiological analysis, mutant strain and other complex situations. Though high altitudes may decrease the transmission risk of COVID-19, the mentioned populations should be considered especially for COVID-19 due to technical errors and canceled ventilation of commercial ventilators in high-altitude regions (Brevoort et al., 2020).

5. Conclusion

This study revealed the relationship between altitude and COVID-19 infection in China via nonlinear regression, spearman regression analysis, and mediating effect model. Environmental factors, such as mitigation scale index, ambient temperature, absolute humidity, diurnal temperature range, SO2, and CO partially mediated 44.7% of the correlation between altitudes and COVID-19 infection. The mentioned evidences present more insights into the altitude-mediated COVID-19 transmission mechanism.

Credit author statement

Peizhi Song: Conceptualization, Data curation, Formal analysis, Writing – original draft. Huawen Han: Methodology, Supervision, Writing – review & editing. Hanzhong Feng: Software, Supervision, Validation. Tuoyu Zhou: Formal analysis, Investigation, Validation. Wenbo Meng and Yitian Fang: Investigation, Software, Methodology. Jun Yan, Junfeng Li and Pu Liu: Writing – review. Yun Hui, Xun Li and Xiangkai Li: Conceptualization, Formal analysis, Resources, Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

Arias-Reyes, C., et al., 2020a. Decreased Incidence, Virus Transmission Capacity, and Severity of COVID-19 at Altitude on the American Continent. Arias-Reyes, C., et al., 2020b. Does the pathogenesis of SARS-CoV-2 virus decrease at high-altitude? Respir. Physiol. Neurobiol. 277, Bai, X., et al., 2014. Society: realizing China’s urban dream. Nature 509, 158–160. Bashir, M.F., et al., 2020. Correlation between climate indicators and COVID-19 pandemic in New York, USA. Sci. Total Environ. 728, 138835, Berendt, R.F., et al., 1971. Virucidal properties of light and SO2. II. Effect of a low gas concentration on aerosolized virus. PSEBMC (Proc. Soc. Exp. Biol. Med.) 138, 1005–1008, Berendt, R.F., et al., 1972. Virucidal properties of light and SO2. I. Effect on aerosolized Venezuelan equine encephalomyelitis virus. PSEBMC (Proc. Soc. Exp. Biol. Med.) 139, 1–5, Boedde, P.I., et al., 2011. Transmission parameters of the A/H1N1 (2009) influenza virus pandemic: a review. Influenza and other respiratory viruses 5, 306–316, Boomshower, S.R., et al., 2022. A review and analysis of personal and ambient PM2.5 measurements: implications for epidemiology studies. Environ. Res. 204, 112019, Brevoort, A., et al., 2020. High-altitude populations need special considerations for COVID-19. Nat. Commun. 11, 5280, Cadnum, J.L., et al., 2020. Effectiveness of ultraviolet-C light and a high-level disinfection cabinet for decontamination of N95 respirators. Pathog Immun 5, 52–67, Cano-Pérez, E., et al., 2020. Negative correlation between altitude and COVID-19 pandemic in Colombia: a preliminary report. Am. J. Trop. Med. Hyg. 103, 2347–2349, Cao, X., 2020. COVID-19: immunopathology and its implications for therapy. Nat. Rev. Immunol. 20, 269–270, Cma, 2021. Data available from the NCMA/CMAs data.cma.cn/. da Costa, A.C.C., et al., 2018. Spatiotemporal diffusion of influenza A (H1N1): starting point and risk factors. PLoS One 13, e0202822, Dantas, G., et al., 2020. The impact of COVID-19 partial lockdown on the air quality of the city of Rio de Janeiro, Brazil. Sci. Total Environ. 729, Fang, F., et al., 2020. Human mobility restrictions and the spread of the Novel Coronavirus (2019-nCoV) in China. J. Publ. Econ. 191, 104272, Feng, Z., et al., 2015. Ground-level O3 pollution and its impacts on food crops in China: a review. Environ. Pollut. 199, 42–48, Fu, L., et al., 2020. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and meta-analysis. J. Infect. 80, 656–665, Goyal, P., et al., 2020. Clinical characteristics of COVID-19 in New York city. N. Engl. J. Med. 382, 2372–2374, Grant, W.B., et al., 2020. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 12 (4), 988, Gupta, A., et al., 2020. Significance of geographical factors to the COVID-19 outbreak in India. Modeling Earth Systems and Environment 6, 2645–2653, Han, H., et al., 2019. Improvements of thermophilic enzymes: from genetic modifications to applications. Bioresour. Technol. 279, 350–361, Han, S., et al., 2011. Analysis of the relationship between O3, NO and NO2 in Tianjin, China. Aerosol Air Qual. Res. 11, 128–139, Hindson, J., 2020. COVID-19: faecal-oral transmission? Nat. Rev. Gastroenterol. Hepatol. 17, 259.
