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PII: S0013-9351(22)00541-2

DOI: https://doi.org/10.1016/j.envres.2022.113214

Reference: YENRS 113214

To appear in: *Environmental Research*

Received Date: 11 November 2021

Revised Date: 24 March 2022

Accepted Date: 25 March 2022

Please cite this article as: Song, P., Han, H., Feng, H., Hui, Y., Zhou, T., Meng, W., Yan, J., Li, J., Fang, Y., Liu, P., Li, X., Li, X., High altitude Relieves transmission risks of COVID-19 through meteorological and environmental factors: Evidence from China, *Environmental Research* (2022), doi: https://doi.org/10.1016/j.envres.2022.113214.

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, Wring-review & editing, Supervision, Funding acquisition.

High Altitude Relieves Transmission Risks of COVID-19 through Meteorological and Environmental Factors: Evidence from China

Peizhi Song [a#], Huawen Han [a#], Hanzhong Feng [a], Yun Hui [a], Tuoyu Zhou [a], Wenbo Meng [b],

Jun Yan [b], Junfeng Li [b], Yitian Fang [c], Pu Liu [b], Xun Li [b]*, Xiangkai Li [a]*

[a]Gansu Key Laboratory of Biomonitoring and Bioremediation for Environmental Pollution, School of Life Sciences, Lanzhou University, Tianshui South Road #222, Lanzhou, Gansu 730000, PR China

[b]Key Laboratory for Biological Therapy and Regenerative Medicine Transformation Gansu Province, Lanzhou, P.R. China;

[c]State Key Laboratory of Microbial Metabolism, School of Life Sciences and Biotechnology, Shanghai Jiao Tong University, Shanghai 200240, China

[#] These authors contributed equally to this work

* Corresponding author:

Xiangkai Li, Ph.D.

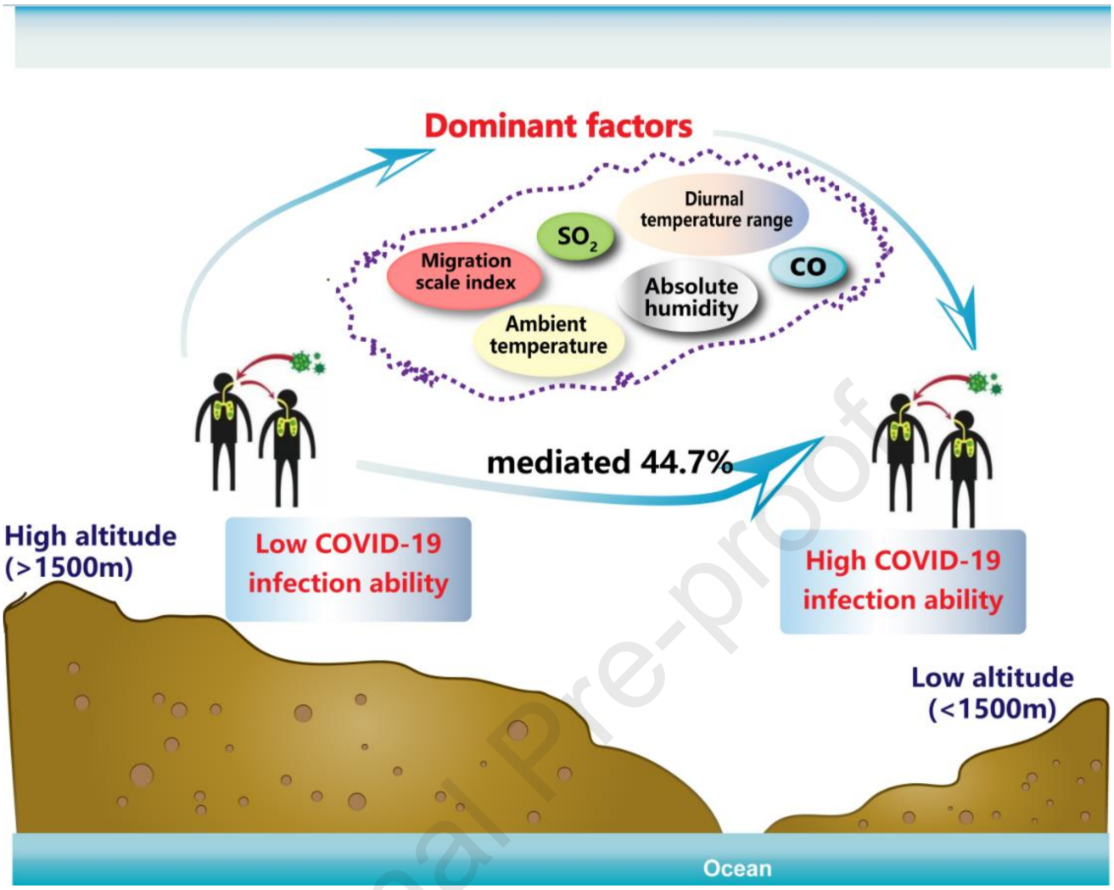
Ministry of Education Key Laboratory of Cell Activities and Stress Adaptations, School of Life Science, Lanzhou University, Tianshui South Road #222, Lanzhou, Gansu 730000, People's Republic of China.

Phone: +86-931-8912560

Fax: +86-931-8912561

E-mail: xkli@lzu.edu.cn

Graphical Abstract



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 SO_2 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 SO_2, CO, and DTR. Subsequent mediating effect model with altitude-correlated factors, such as mobility, AT, AH, DTR and SO_2, 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.

Key words: COVID-19, environmental factors, altitude, mediating effect model, 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 meters 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 in high-altitude regions (Arias-Reyes et al., 2020b; Cadnum et al., 2020). Low pressure in high-altitude regions also affected lung physiology (Breevoort 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 (Yue 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; Lian 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 been also 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, 2020, the National Health Commission of the People's Republic of China (NHC) released the local cases of COVID-19 in China while the local cases of Argentina derives from the Johns Hopkins Coronavirus Resource Center (Hopkins, 2021) (ii) During March 2, 2020 to May 10, 2021, the local cases of COVID-19 infection were compiled from the NHC(NHC, 2021), which distinguished the local cases from the imported cases of COVID-19 on each day.

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 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 nCOV2019 (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 ArcGIS10.7.

2.3 Statistic analysis

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, AT, AH, DTR and mobility) have no effect on COVID-19 confirmed cases change.

$H4_0$: Altitude has no mediating effect on COVID-19 transmission by changing environmental factors.

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, NO_2, PM2.5, PM10, SO_2, O_3, 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 10000. 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 $H1_0$ 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.

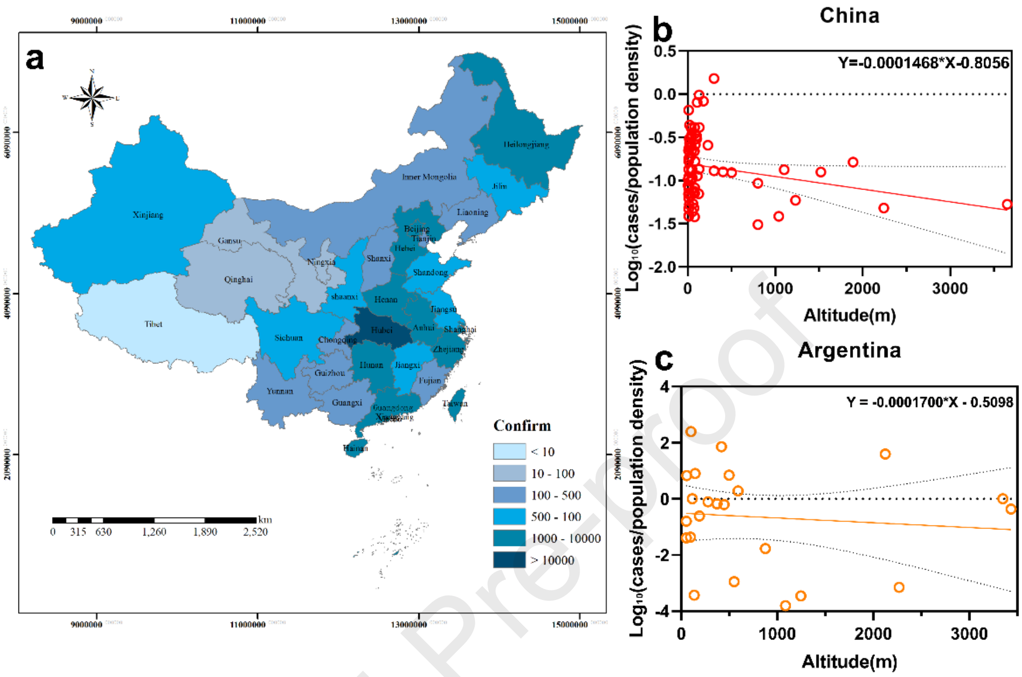


Fig. 1. a, Geographic patterns of COVID-19 confirmed cases from China as of May 31, 2020; b, c, linear correlation analysis between altitudes and infection rate of COVID-19 in China (b) and Argentina (c)

3.2 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 SO_2 and DTR as compared to the low-altitude regions, (Fig. 2). The change in altitudes has no significant impact on the PM10, CO, O_3, and NO_2 ($p>0.05$). Among all parameters, air pollutants SO_2 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, SO_2, 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, NO_2 and O_3. Collectively, this findings disproved $H2_0$ hypothesis, namely, altitude has a significant correlation with environmental factors except for NO_2 and O_3.

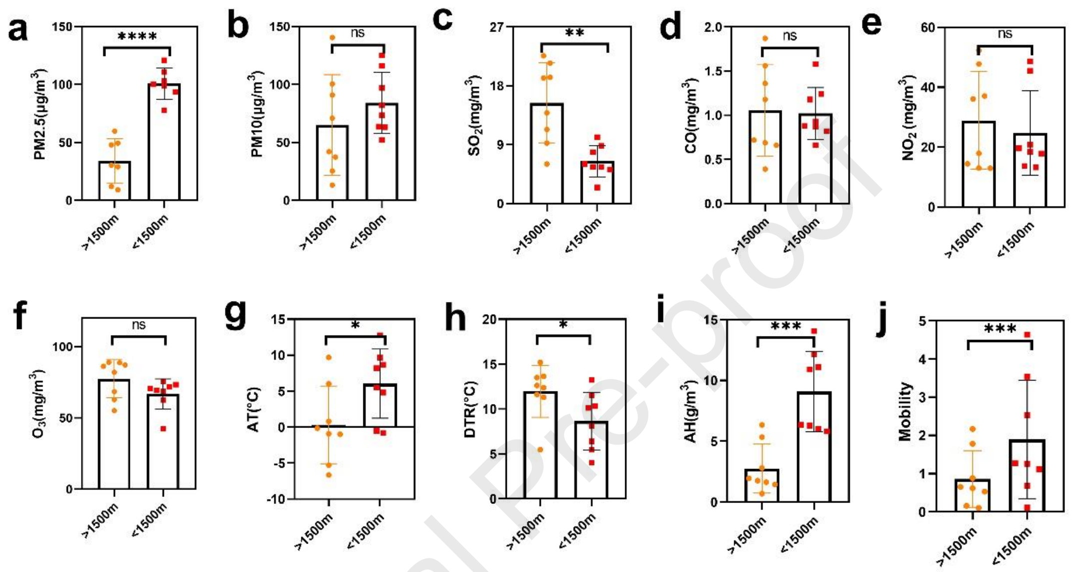


Fig. 2. Comparative analysis of air pollutants, climate factors and social factors from low-altitude region (<1500 m) and high-altitude region (>1500 m). AT: ambient temperature; AH: absolute humidity; DTR: diurnal temperature range. * represents significant difference while ns indicates no significant difference. * *P*<0.05, ** *P*<0.01, * *P*<0.001.**

Table 1 Correlation analysis of altitude and environmental factors

Factor	correlation index(r)	P value
PM2.5	0.244*	0.036
PM10	0.291*	0.012
SO_2	0.475***	<0.001
CO	0.442***	<0.001
NO_2	0.104	0.376
O_3 8h	-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. "***" and "*" represent $p<0.001$ and $p<0.05$, respectively.

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.

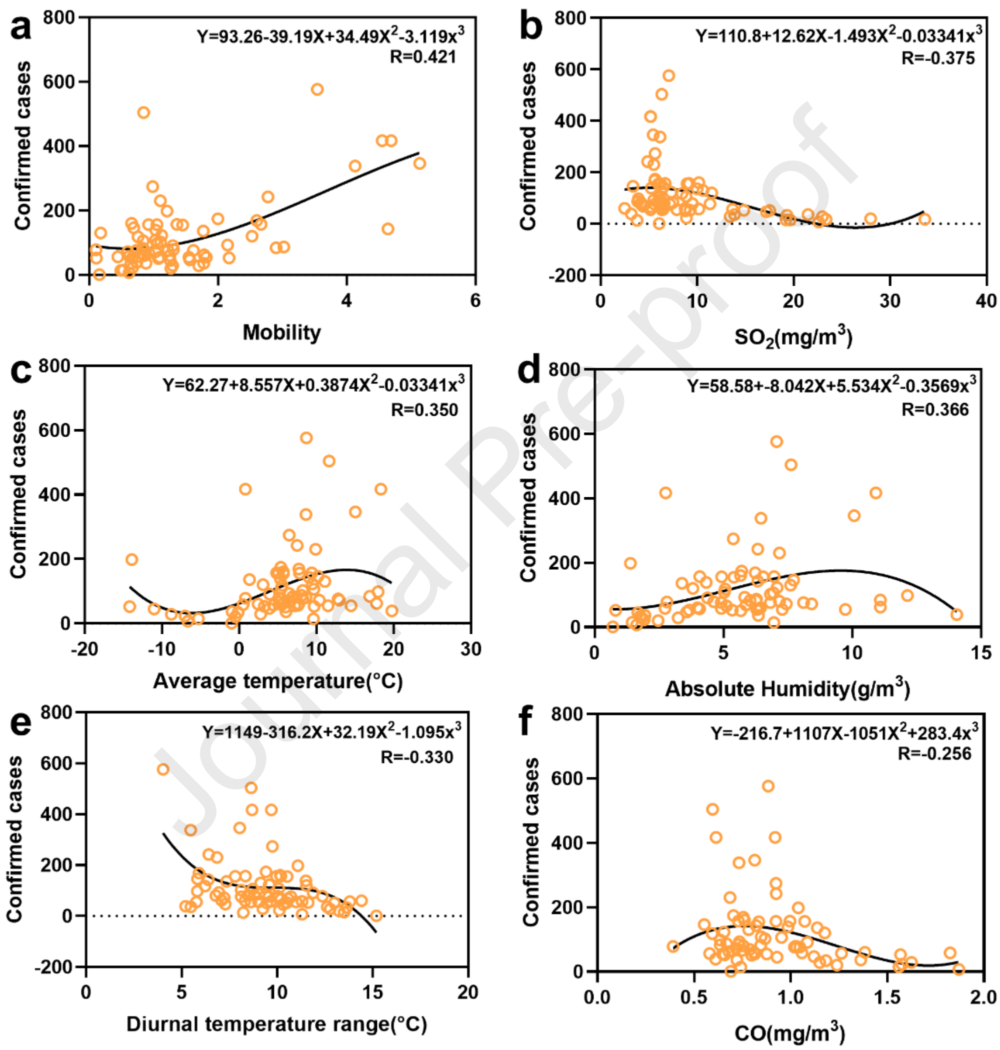


Fig. 3. Spearman correlation analysis between environmental factors and COVID-19 confirmed cases. Mobility (a); Air pollutants: SO_2 (b), CO (f); Climatic parameters: Average temperature (c), absolute humidity (d), diurnal temperature range (e).

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 decrease in confirmed cases; whereas COVID-19 infection dramatically increased when the mobility exceeded 2.

3.3.2 AT, DTR, AH, CO and SO_2 are secondary factors responsible for COVID-19 infection

An obvious S-shaped curve was observed between environment factors (AT, SO_2) and COVID-19 confirmed case (Fig.3b,3c). The level of SO_2 has a negative correlation with confirmed cases above a threshold of 8 $\mu g \cdot m^{-3}$, and then confirmed cases rebounded near 25$\mu g \cdot m^{-3}$. However, AT ranging from 0 to 15 ℃ exhibited a positive correlation with confirmed cases while AT below 0 ℃ showed a low distribution of COVID-19 infection (Fig.3c). Unlike SO_2, 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 $mg \cdot m^{-3}$. Similarly, COVID-19 confirmed cases increased first and then decreased with the changes of AH (Fig. 3d), its corresponding threshold values was 6 $g \cdot m^{-3}$. 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 $H3_0$ hypothesis because environmental factors (e.g. mobility, AT, DTR, AH, CO and SO_2) have an impact on COVID-19 confirmed cases.

3.3.3 O_3, NO_2, PM2.5 and PM10 have no impact on COVID-19 infection

In the mentioned parameters, other factors (e.g., O_3, NO_2, 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 $mg \cdot L^{-1}$ 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 (IE = -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 $H4_0$ hypothesis (Fig. 1). These evidences suggest that the altitude can influence COVID-19 infection by changing corresponding environmental factors.

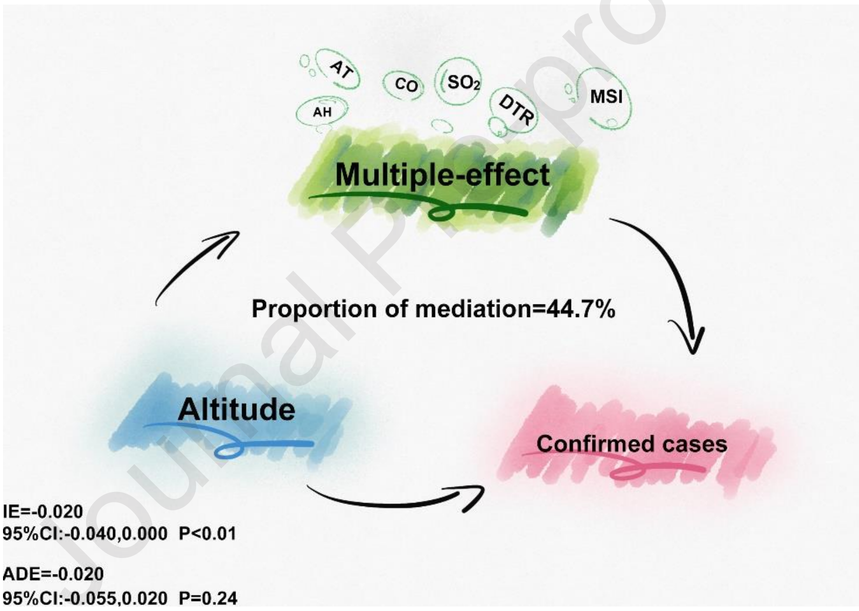


Fig.4. Multiple mediating effect model between altitude and confirmed cases. AT: ambient temperature; AH: absolute humidity; DTR: diurnal temperature range.

Table 2 A mediating effect between infected rates and altitude

Factor	IE	ADE	Total Effect
SO_2	-0.010(-0.026,0.000)*	-0.029(-0.063,0.010)	-0.038(-0.075,0.000)**
CO	-0.002(-0.012,0.010)	-0.040(-0.075,0.000)**	-0.042(-0.084,-0.010)**
Mobility	-0.020(-0.045,0.010)	-0.019(-0.049,0.010)	-0.040(-0.071,0.010)
AT	-0.010(-0.025,0.000)*	-0.031(-0.062,0.010)	-0.041(-0.074,0.000)**
DTR	-0.007(-0.021,0.010)	-0.035(-0.078,0.010)	-0.042(-0.082,0.000)***
AH	-0.012(-0.027,0.000)*	-0.029(-0.064,0.010)*	-0.041(-0.072,-0.010)***

Note: AT: ambient temperature; AH: absolute humidity; DTR: diurnal temperature range. '***' : P<0.001, '**': P<0.05. '*': P<0.1.

4 Discussion

4.1 Altitudes 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-Ramirez 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 (Ivashkiv, 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 study demonstrated that the concentration of PM 2.5 was altitude-dependent due to fewer developed urban agglomerations in high altitudes. Such trend can be supported by Zhao et. al., reported that a higher PM2.5 level in urban centers (Zhao et al., 2014). COVID-19 broke out in winter, and abundant particulate pollutants (e.g., PM10) increased due to the prevalence of winter heating, especially in Northwest regions of China (e.g., Shaanxi, Gansu and Ningxia) (Qu et al., 2010). With the promulgation of national environmental protection policies, the total emission of SO_2 was effectively controlled (Jiang et al., 2020). Nevertheless, high-altitude regions required extra fossil fuel combustion for warming, thereby causing higher SO_2 concentration than that in low-altitude regions. For O_3, NO_2 and CO, high population density could be a main contributor for their emissions (Feng et al., 2015; Han et al., 2011). The present observations revealed a significant difference of AT, AH, and DTR between high- and low-altitude regions due to their distinct climate types. High-altitude regions pertain to temperate continental climate and plateau climate, while monsoon climate is prevalent in low-altitude regions (Shi et al., 2007)

4.3 Environmental factors influence the COVID-19 transmission

Environmental factors and social customs contribute to the transmission of some representative pandemic viruses (Boomhower et al., 2022). Among of these factors, mobility is dominant factor to control the human-to-human transmission risk of COVID-19 (Jiang and Luo, 2020; Liu et al., 2020), as well as SARS (Li et al., 2005) and H1N1(Boëlle et al., 2011). It is estimated that confirmed cases increased by 105.27% without Wuhan blockade based on the prediction model (Wuhan 2020 vs. seven other lockdown cities 2020). In contrast, strict city lockdown and home quarantine order decreased the migration rate by 54.15% (Fang et al., 2020). Although low mobility is accompanied with less social contact (Zhu et al., 2020c), some unexpected events (e.g., George Floyd) and large festival (e.g., Kumbh Mela) led to an explosion in of new confirmed cases (Valentine et al., 2020; Visaria and Dharamdasani, 2021). For example, 5-day abnormal growth were observed in all six cities surveyed, including Atlanta (4.24%), Houston (16.76%), Jacksonville (32.35%), Miami (8.3%), Orlando (51.75%), and Phoenix (4.26%). This COVID-19 rebound is largely attributed to high mobility and large gatherings in the absence of safe social distancing. China's current prevention and control measures effectively reduced the spread of COVID-19, but travel restrictions should still be maintained (Zhao et al., 2020). Similar government interventions were enacted in Peru, Bolivia, and Colombia, and people’s time at home increased by 50%. This low mobility has significantly restricted the spread of COVID-19 (Zhu et al., 2020a).

Our studies confirmed that AT, AH and DTR affected the COVID-19 infection, in lined with aerosol mediated person-to-person 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 hours. 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., SO_2 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 SO_2 gas and 308 $cm^{-2} \cdot min^{-1}$ of simulated solar radiation kill Encephalomyelitis viral (Berendt et al., 1971; Berendt et al., 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 accidence of emphysema D (Mendes et al., 2019). Thus, we speculated that low vitamin D at high-latitude regions a potential contribution to decreaseing 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 nucleomyces spores and other factors into PM2.5 and PM10 to avoid the deviation caused by a single factor.

4.5 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 underestimates 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., SO_2, 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.

4.6 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 (Breevoort 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, SO_2, 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.

Acknowledgments

This work was supported by the National Natural Science Foundation Grant (No: 31870082), Gansu province major Science and Technology projects (No: 17ZD2WA017), and Fundamental Research Funds for the Central Universities grant (No: lzujbky-2019-cd01, lzujbky-2020-pd06, No. lzujbky-2020-30).

Conflict interest

The authors declare no conflict of interest.

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Highlights

- High altitudes reduce the COVID-19 infection.
- Altitude changes the levels of MSI, DTR, AH, AT, and SO_2.
- Multiple mediating model confirmed altitude-dependent COVID-19 infection.

Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: