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The Impact of Smoking on COVID-19 Analyzed by Hierarchical Linear Model

Chia-Chang CHUANG[1], Maria Dyah KURNIASARI[2], Min-Sun KIM[3]*, Andrian Dolfriandra HURUTA[4]

Abstract

COVID-19 has been of great concern since it broke out. Many countries have put more effort into securing vaccines and therapeutic medicines. In the meantime, there has been a large number of scholarly efforts in figuring out the relationship between smoking and new coronary pneumonia. This study firstly collected daily data (the number of people hospitalized with new coronary pneumonia, severe cases, and the number of people double-vaccinated against new coronary pneumonia in various countries or regions) and annual data (the human development index and smoking rate of each country or region). We collected data from 160 countries from the Our Data World database. The time is for January 1, 2020 through June 30, 2022. We divided daily and annual data into the first-level and second-level data. Finally, we checked the relationship between smoking and COVID-19 in a Hierarchical Linear Model (HLM). The result shows that smoking raises the number of new cases of infection and death among people fully vaccinated per hundred. There is a partial mediating effect of new cases smoothed per million over new deaths smoothed per million. Smoking significantly increases the effect of new cases smoothed per million over new deaths smoothed per million. Our findings have high generalizability around the world.

Keywords: COVID-19; smoking; nicotine; ACE2; nAChR; HLM.

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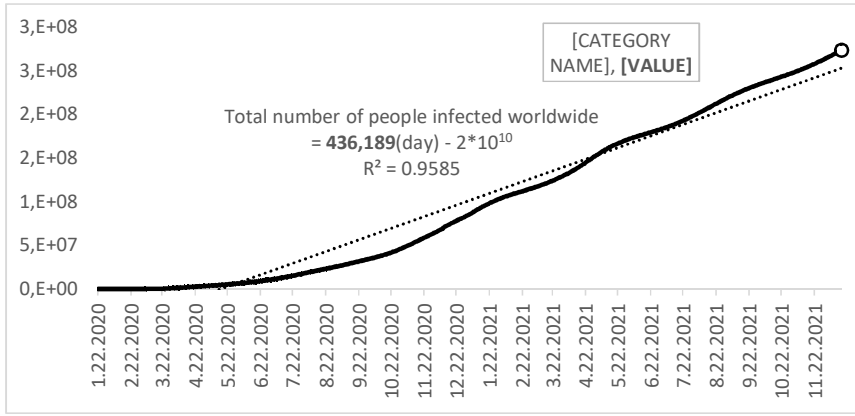
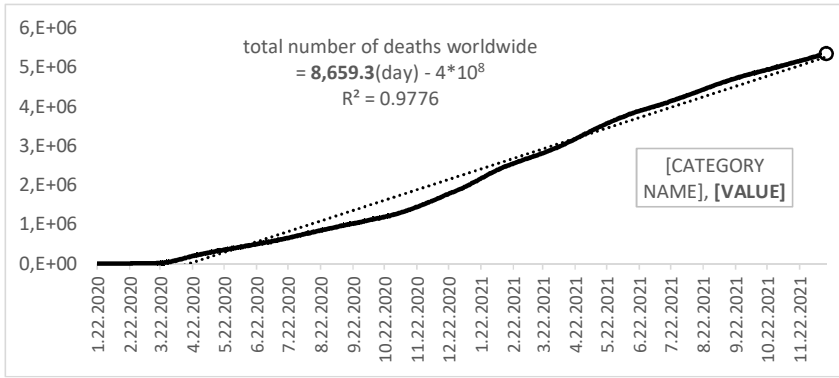
Introduction

This subsection begins with an overview of coronavirus (COVID-19) and observes the impact of the pandemic on the global economy in the literature. While doing so, this study provides the key issue of the impact of smoking on new coronary pneumonia. According to the Our World in Data (2022) database for January 22, 2020 through December 17, 2021, the cumulative number of confirmed cases of new coronary pneumonia (COVID-19) in the world has reached 273,668,314, about 3.46% of the global population, higher than the casualty rate of 3% in World War II (Clodfelter, 2017). An average daily increase of 436,189 is shown in Figure 1.



Source: Our World in Data (2022), author's own compilation.

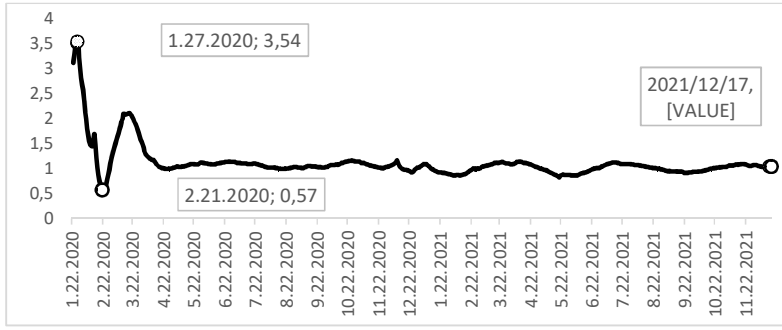
Figure 1. Time trend of cumulative confirmed cases of COVID-19 globally (unit: person).



Source: Our World in Data (2022), author's own compilation.

Figure 2. Time trend chart of cumulative deaths from COVID-19 worldwide (unit: person).

In order to prevent further spread of the epidemic, various countries have developed various vaccines (Handayani *et al.*, 2022). As of December 17, 2021, the World Health Organization (WHO) has approved 10 vaccines including BioNTech produced by Pfizer Pharmaceuticals based on urgent needs (Our World in Data, 2022). In terms of vaccination, as of December 17, 2021, the "Our Data World" database indicated that a total of 8,672,704,087 doses have been provided globally, and that around 46.83% of world population have completed their second vaccination. However, spread of new coronary pneumonia has no signs of slowing down. Figure 3 shows a time trend of the global reproduction rate moving from the highest point of 3.54 on January 22, 2020 to the lowest point of 0.57 on February 22, 2020. When it comes to the overall trend, the contagion rate illustrates a slight fluctuation around 1 to December 17, 2021 (1.04).

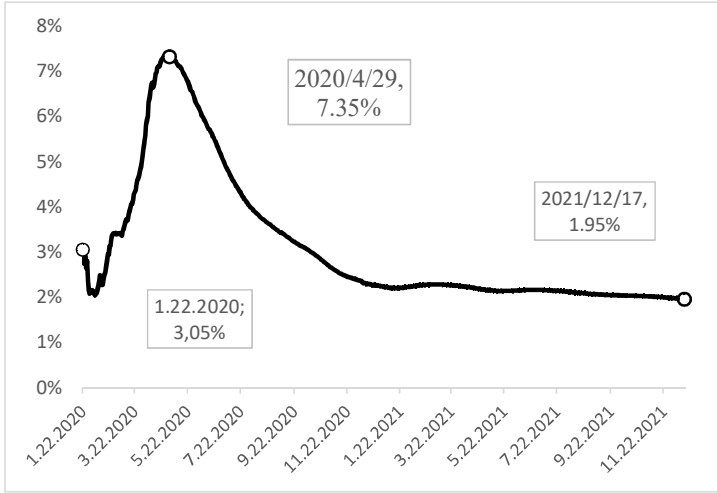


Source: Our World in Data (2022), author's own compilation.

Figure 3. Time Trend of global reproduction rate

According to Heesterbeek (2002), a contagion rate of less than 1 means that the contagious cases are gradually reduced. A contagion rate of greater than 1 denotes that contagious cases spread exponentially, and that it becomes an epidemic. But The situation could not last forever. The number of infected populations slowly decreases. Because some of the population could die from contagion, and some could build their own immunity system after contagion. Contagion rate of 1 shows that contagion comes to an epidemic. Empirical data in Figure 3 illustrates continuation of the COVID-19 epidemic.

Mortality rose from 3.05% on January 22, 2020 to a peak of 7.35% on April 29, 2020, and then it plummeted in late January of 2021. After that time, the line shows a stable movement to December 17, 2021, as shown in Figure 4.



Source: Our World in Data (2022), author's own compilation.

Figure 4. Time trends in global COVID-19 mortality rates

Figure 1 and 2 show the cumulative number of confirmed cases and deaths from new coronary pneumonia in the world. In Figure 3, contagion rate generally shows a slight fluctuation around 1. The mortality rate in Figure 4 comes to 1.95% after a wide range of movement. Countries put decisive measures to prevent epidemic from spreading. Although the effect of some control has been achieved, it has also paid a huge price. World Bank's (2022) database shows that the global GDP growth rate in 2020 is -3.59%. The figure is almost twice as low as the recession of -1.67% caused by the financial tsunami in 2009.

There is currently much discussion about the economic impact of COVID-19. Filgueira and Lo Vuolo (2020) noted that COVID-19 has weakened social system in Latin American countries. It turns out that measures of protecting people from being infected have had a negative impact on economic growth. Gopalan and Misra (2020) noted that a large-scale city called for closure measures to prevent the spread of new crown pneumonia, and that it brought negative effects on social system. Its impact ranges over all aspects of society. It is widely believed that the global economy has been experiencing unprecedented challenges by COVID-19 (Zhao & Rasoulinezhad, 2021).

It says that COVID-19 is a major issue in early 2000s. Previous research papers found that COVID-19 can be transmitted through droplets (Buonanno *et al.*, 2020; Falahi & Kenarkoohi, 2020; Stadnytskyi *et al.*, 2020). The target is respiratory system, especially lower respiratory system and lung (Conti *et al.*, 2020; Contini *et al.*, 2020). But pathophysiology of pneumonia is poorly checked (Fogarty *et al.*, 2020). Therefore, numerous studies have attempted to explore a relationship between smoking behavior and COVID-19. Some research papers suggest that smoking worsens symptoms of COVID 19 (Cai, 2020; Kabbani & Olds, 2020; Smith *et al.*, 2020). Some other research papers suggest that smoking could relieve COVID-19 symptoms (Kloc *et al.*, 2020; Tajlil *et al.*, 2020; Tizabi *et al.*, 2020). Gupta *et al.* (2021) reviewed 144 studies about a relationship between smoking and new coronary pneumonia, but still could not reach a definite conclusion.

Edwards and Munafò (2020) noted that many existing literatures on the relationship between smoking and new coronary pneumonia are still at a very preliminary stage or only limited to speculative judgments. Many assumptions and uncertainty abound. Thus, this study attempts to identify the relationship between smoking and new coronary pneumonia. The extensive country data about smoking population rates and COVID-19 hospitalizations including serious cases are collected from the World Bank and Our World in Database.

The literature Review and Hypothesis Development

This section checks related literature about how smoking affects COVID-19 patients and compares the literature of which smoking worsens the symptom of COVID-19 to the literature of which smoking alleviates the symptoms of COVID-19.

Smoking behavior and COVID-19

Countries have invested a lot of resources to figure out the relationship between smoking and COVID-19, and many scholars have also focused on the study to check whether those patient group is prone to critical illness. Gong *et al.* (2020) collected 44,500 confirmed cases. Around 15.8% cases were developed to serious condition, and the consequence led to a higher mortality rate (Gong *et al.*, 2020; Quah *et al.*, 2020; Routsi *et al.*, 2020). Smoker has a higher chance of being exposed to nicotine, and nicotine causes the severe acute respiratory syndrome coronavirus 2 (hereinafter referred to as: SARS-CoV-2). It leads confirmed patients to severe illness. It supports that smokers are prone to severe illness after contracting new coronary pneumonia (Kabbani & Olds, 2020; Purkayastha *et al.*, 2020; Raspe *et al.*, 2021).

Dratcu and Boland (2020) found that a heavy tobacco user fully recovered from new coronary pneumonia. They suggested that nicotine could prevent the excessive production of pro-inflammatory cytokines from new coronary pneumonia (Dratcu & Boland, 2020). Smokers are less likely to be hospitalized with COVID-19 (Farsalinos *et al.*, 2020a; Farsalinos *et al.*, 2020b). An interaction between the nicotinic cholinergic system and nicotine has potential medical uses in treating COVID-19 (Tizabin *et al.*, 2020; Gauthier *et al.*, 2021). From the above, it is clear that there are different perspectives between smoking and new coronary pneumonia. In the following part, this study observes the literature on which smoking worsens symptoms of new coronary pneumonia and checks the literature on smoking alleviates symptoms of new coronary pneumonia.

Smoking worsens COVID-19

Some literature suggests that angiotensin-converting enzyme 2 (ACE2) is a receptor on cell membrane, whose role allows SARS-CoV-2 to move to respiratory epithelial cells (Heijink, *et al.*, 2021; Kabbani & Olds, 2020; Li *et al.*, 2021). As ACE2 receptors increase, smoking worsens symptoms of patients with COVID-19 (Heijink, *et al.*, 2021; Kabbani & Olds, 2020; Li *et al.*, 2021). Smoking COVID-19 patients is prone to serious illness in comparison to non-smoking COVID-19 patients (Cai, 2020; Li *et al.*, 2021;

Patanavanich & Glantz, 2020). Some research papers found that progression of smoking COVID-19 patients is much faster than that of non-smoking COVID-19 patients (Mahabee-Gittens *et al.*, 2021; Peng *et al.*, 2021; Prats-Uribe *et al.*, 2021). Purkayastha *et al.* (2020) told that the disease progression or mortality of smoking and non-smoking patients is dictated by demographic factors (race, gender, age, and degree of chronic disease). They also found that the number of being infected cells increased significantly after being exposed to cigarette smoke (Purkayastha *et al.*, 2020). Liu *et al.* (2021) found that mice exposed to five cigarettes four times a day had a significant increase in ACE2. It shows that smoking patients have more opportunities to deteriorate their symptoms. COVID-19 patients who have long-term accumulation of nicotine suffer from many adverse impacts (Raspe *et al.*, 2021; Vardavas & Nikitara, 2020).

H1: When a country has a higher rate of smokers, it brings a higher contagion rate of COVID-19, and it leads to a high death rate.

Smoking reduces COVID-19

Some literature suggests that nicotine in tobacco plays an important role in alleviating symptoms of COVID-19 (Changeux *et al*., 2020). Changeux *et al*. (2020) found that nicotine-type acetylcholine leads to frequent loss of smell and neurological symptoms (headache, nausea, vomiting) in COVID-19 patients. Nicotinic acetylcholine receptor (hereinafter referred to as nAChR) is a pathway. Nicotine fights SARS-CoV-2 attaching to nAChR to block SARS-CoV-2 from entering nAChR. It brings a slowdown in spread of coronavirus. Farsalinos *et al.* (2020) suggested that process of nicotine in the body against COVID-19 includes anti-inflammatory effects. It promotes nicotine patch therapy for non-smoking COVID-19 patients (Tindle *et al.* 2020). There is case study that a frail 63 years old Caucasian British man with COVID-19 had a heavy smoking history, and that he recovered from COVID-19 after nicotine therapy (Dratcu & Boland, 2020). He used nicotine patches (21 mg/day), inhalers (15 mg cartridges, 6 cartridges/day), and e-cigarettes (a box of 3 ml/day) for COVID-19 treatment (Dratcu & Boland, 2020). During the nicotine treatment, there were no mechanical respiratory supports (Dratcu & Boland, 2020). Farsalinos *et al.* (2020) found that SARS-CoV-2 induces an immune storm (a phenomenon in which pro-inflammatory cytokines rise in response to the infection). It brings serious organ damage or even death (Farsalinos *et al.*, 2020). Nicotine activates immune system and relieves the intensity of cytokine storms (Farsalinos *et al.*, 2020). It alleviates symptoms of new coronary pneumonia (Farsalinos *et al.*, 2020). Farsalinos *et al.* (2020) noted that current smoking rate among hospitalized COVID-19 patients is low, and that it is not enough to make smoking treatment measures. Nicotine has a protective effect against COVID-19, but it could be masked by other related effects from smoking (Farsalinos *et al.*, 2020). Hospitalization generally does not allow smoking. Further observation is needed concerning this matter.

Tizabin *et al.* (2020) claimed that smoking has many negative effects on the human body, especially the respiratory system and cardiovascular systems. COVID-19 Patients with respiratory or cardiovascular disease are prone to more serious illnesses (Tizabin *et al*., 2020). But the interaction between the nicotinic cholinergic system and ACE2 is used for various neuropsychiatric and neurodegenerative diseases. In this regard, it is probable that nicotine has potential use in the treatment of new coronary pneumonia (Tizabin *et*

al., 2020). Tizabin *et al.* (2020) claimed that smoking cessation could lead to harmful effects on people with COVID-19. Smoking plays a potential therapeutic role in nicotine cholinergic receptors. Nicotine-related factors tackle SARS-CoV-2 entry.

According to forty-one international studies about COVID-19 symptom between smoking and non-smoking patients, although smoking increases the risk of worsening COVID-19 symptoms, nicotine in cigarette has anti-inflammatory effects to treat the symptom (Gauthier *et al.*, 2021). It strengthens cholinergic anti-inflammatory pathway by stimulating nicotine-type acetylcholine receptors (Borovikova *et al.*, 2000). Given these evidences, it is clear that nicotine has a therapeutic effect on new coronary pneumonia.

H2: When a country has a higher rate of smokers, it brings a lower contagion rate of COVID-19, and it leads to a low death rate.

The literature integration

Most of the literature do not agree with protective effects of smoking on new coronary pneumonia. Rather, there are different views on nicotine produced by smoking. Some study papers claimed that harmful substances generated by smoking worsen symptoms of new coronary pneumonia. On the other hand, some other study papers noted that nicotine in cigarettes intervene in immune system to ease cytokine storm. Thus, COVID-19 symptoms of smokers are relieved. It shows that there are some contradictory research papers in the relationship between smoking and development of COVID-19 diseases.

This study employs relevant data on new coronary pneumonia to examine the relationship between smoking and COVID-19. Data are collected from three major databases (Our World in Data, the United Nations Development Programme, and the World Bank Database). Daily data on COVID-19 is from Our World of Data, Annual data on Human Development Index (HDI) is from the United Nations Development Programme, and annual smoking data for each country is from World Bank Database.

Methodology

This section first sorts out sample types and research methods in the past literature and then explains sample data types and appropriate research methods.

From the review of the literature, we can know that there are two perspectives in the literature concerning nicotine by smoking. One is that nicotine increases ACE2 receptor, allowing of entry of the new coronavirus SARS-CoV-2 into host cells and replication. It shows that smoking worsens COVID-19 (Heijink *et al.*, 2021; Kabbani & Olds, 2020; Li *et al.*, 2021; Mahabee-Gittens *et al.*, 2021; Peng *et al.*, 2021; Prats-Uribe *et al.*, 2021). Another is that nicotine-type acetylcholine (nAChR) receptor and the ACE2 receptor serve as pathway. And that nicotine binds SARS-CoV-2 to nAChR blocking SARS-CoV-2. The nAChR leads to a protective effect that delays new coronary pneumonia. Nicotine facilitates functioning of the immune system. Therefore, symptoms of new coronary pneumonia in smoking patients are relatively weak (Changeux *et al.*, 2020; Dratcu & Boland, 2020; Gauthier *et al.*, 2021; Farsalinos *et al.*, 2020; Tindle *et*

al., 2020).

Basically, empirical research methods of the literature can be divided into six categories:

Case study method

A case study is an observation method from psychology or medicine. It aims to observe and understand an individual case to record complete course of the case in detail. In the literature, a smoker diagnosed with COVID-19 was observed in detail, while nicotine therapy was conducted. In the meantime, the patient's daily changes were recorded to understand the impact of smoking on COVID-19 (Dratcu & Boland, 2020).

Maternal proportional difference test method

This method is to firstly collect case data of patients with new coronary pneumonia, then to compare severe cases of the smoking group to severe cases of the non-smoking group in proportion, and finally to observe the difference between the two groups (Cai, 2020; Li *et al.*, 2021; Patanavanich & Glantz, 2020). This approach is fairly intuitive and straightforward.

Regression analysis

This method is to firstly collect case data of patients with new coronary pneumonia, then to observe the effect of smoking on symptoms with regression analysis. Cox regression, logistic regression, and Poisson regression were used to examine the effects of smoking on disease progression (Mahabee-Gittens *et al.*, 2021; Peng*et et al.*, 2021; Prats-Uribe *et al.*, 2021). Cox regression can apply some factors such as patient age, gender, and race to exploring how smoking affects patient survival. Logistic regression can be used to observe the effect of smoking on the probability of severe illness or death. Poisson regression is often used in case where a dependent variable is an intermittent variable such as the number of severe cases of new coronary pneumonia. It can also be applied to ratio data (the ratio of the number of severe cases of new coronary pneumonia).

Simulation experiment method

In order to control other exogenous variables and to more accurately observe the effect of smoking on the progression of COVID-19, this method firstly cultures human bronchial epithelial cells, and then exposes cells cultured to cigarette smoke to observe any change in the number of infected cells after smoke exposure (Purkayastha *et al.*, 2020).

Animal experiment method

A variety of scientific experiments were conducted with animals to observe the behavioral or physiological response of a specific factor. Consideration of cost forced researchers to use mouse. Mice were exposed to 5 cigarettes 4 times a day to observe changes in SARS-CoV-2 viral receptor ACE2 (Liu *et al.*, 2021).

Integrated analysis

The integrated analysis is to integrate a large amount of professional literature about smoking and COVID-19 for meta-analysis. The integrative analysis is a common research method whenever claims from previous research papers are in discord. It integrates opinions of various researchers and obtains a result that is close to a real situation. When conducting an integrated analysis, a researcher first reads a large number of professional literatures about a related topic and analyzes them with statistical methods to draw a general conclusion (Farsalinos *et al.*, 2020a; Farsalinos *et al.*, 2020b; Gauthier *et al.*, 2021; Raspe *et al.*, 2021; Vardavas & Nikitara, 2020). Sample data of most literature are connected to a certain case or regional hospital or country.

This study aims to observe the relationship between smoking behavior and new coronary pneumonia from a broader perspective. Empirical research is based on data extensively collected. The number of vaccines provided in each country is taken into account. Data is from Our World in Data and the World Bank. Data includes daily and annual data for each country. It makes this study more comprehensive than other related research papers. The relationship between smoking and new coronary pneumonia is observed considering the number of vaccines provided in each country. The number of patients and the number of vaccinations are in daily data. The smoking rate is in annual data. There is a different time set for data. It allows data to use Hierarchical Linear Modeling (HLM) to clarify the relationship between smoking and COVID-19.

This study collects a certain data of 160 countries from the Our Data World database. The time is for January 1, 2020 through June 30, 2022. There are 3 variables: the number of new infections per million of new coronary pneumonia after smoothed (new cases smoothed per million, referred to as NCSPM), the number of new deaths per million of new coronary pneumonia after smoothed (new deaths smoothed per million, referred to as NDSPM), and people who fully received 2 doses of WHO emergency authorization 10 vaccines per hundred (people fully vaccinated per hundred, referred to as PFVPH). This study collects data about the prevalence of smoking (SMOKE) from the World Bank database.

This study employs a cross-level moderated mediation model (multilevel moderated mediation/3M) to observe the influence of SMOKE and NCSPM on NDSPM under the control of PFVPH. Data are fit to the HLM analysis method. A complete 3M test should include three major steps. The first empirical model is a one-way ANOVA with random effects. The second empirical model is the 2-1-1 model (cross-level mediation-lower mediator model) to observe the mediating effect of NCSPM on NDSPM under the control of PFVPH (Mathieu & Taylor, 2007; Krull & MacKinnon, 2001). The intercept model (intercept-as-outcomes regression) is mainly used. Third, the adjustment effects of SMOKE on NCSPM and PFVPH on NDSPM are estimated. The empirical model is a model with randomly varying slopes. The random slope is replaced with SMOKE. To observe the adjustment effect, a more detailed model is set as follows:

Test whether sample data are fit for HLM analysis

One-way ANOVA with random effects is used to test whether sample data are fit for HLM. Since this model is the initial model for HLM analysis, this setting is called the Null model in the literature. Settings of

the Null model are shown in model (0).

Level-1 Model (daily data)

$Y_{ij} = \beta_{0j,null} + r_{ij,null}$ ，$Y_{ij} = NDSPM_{ij}$ 、$NCSPM_{ij}$ 、$PFVPH_{ij}$

Level-2 Model (annual data)

$\beta_{0j,null} = \gamma_{00,null} + u_{0j,null}$

Mixed Model

$Y_{ij} = \gamma_{00,null} + u_{0j,null} + r_{ij,null}$ ，$Y_{ij} = NDSPM_{ij}$ 、$NCSPM_{ij}$ 、$PFVPH_{ij}$ (0)

To check whether sample data are fit for HLM analysis, ICC (intra-class correlation coefficient) is often used as a measure in the literature. ICC is used to identify the degree of similarity among different units in the same group. Its calculation is $V(u_{0j,null})/(V(u_{0j,null})+V(r_{ij,null}))$ from model (0). Cohen (1988) noted that the ICC of greater than 0.059 are fit for HLM analysis. The ICC of greater than 0.138 shows that there is a large difference among groups.

(1) The mediation effect test

The multi-level mediation effect includes 3 stages as shown in Figure 5.

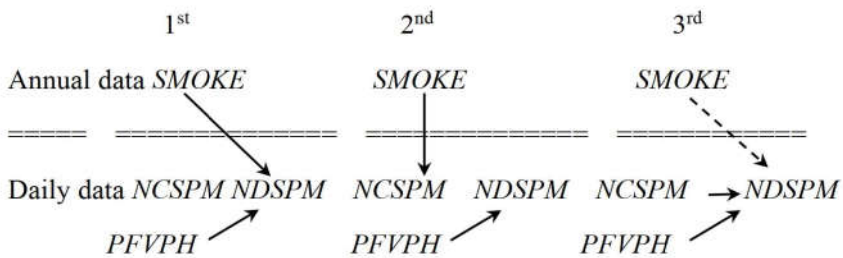


Figure 5. The 3 stages of multi-level mediation effect

The first stage: the impact of SMOKE on NDSPM under the control of PFVPH, as shown in model (1):

Level-1 Model (daily data)

$NDSPM_{ij} = \beta_{0j,1st} + \beta_{1j,1st}*(PFVPH_{ij}) + r_{ij,1st}$

Level-2 Model (annual data)

$\beta_{0j,1st} = \gamma_{00,1st} + \gamma_{01,1st}*(SMOKE_j) + u_{0j,1st}$

$\beta_{1j,1st} = \gamma_{10,1st}$

Mixed Model

$NDSPM_{ij} = \gamma_{00,1st} + \gamma_{01,1st}*SMOKE_j + \gamma_{10,1st}*PFVPH_{ij} + u_{0j,1st} + r_{ij,1st}$ (1)

The second stage: the impact of SMOKE on NCSPM under the control of PFVPH, as shown in model (2):

Level-1 Model (daily data)

$$NCSPM_{ij} = \beta_{0j,2nd} + \beta_{1j,2nd}*(PFVPH_{ij}) + r_{ij,2nd}$$

Level-2 Model (annual data)

$$\beta_{0j,2nd} = \gamma_{00,2nd} + \gamma_{01,2nd}*(SMOKE_j) + u_{0j,2nd}$$

$$\beta_{1j,2nd} = \gamma_{10,2nd}$$

Mixed Model

$$NCSPM_{ij} = \gamma_{00,2nd} + \gamma_{01,2nd}*SMOKE_j + \gamma_{10,2nd}*PFVPH_{ij} + u_{0j,2nd} + r_{ij,2nd} \quad (2)$$

The third stage: controlled by PFVPH, the influence of SMOKE and NCSPM on NDSPM as shown in model 3:

Level-1 Model (daily data)

$$NDSPM_{ij} = \beta_{0j,3rd} + \beta_{1j,3rd}*(NCSPM_{ij}) + \beta_{2j,3rd}*(PFVPH_{ij}) + r_{ij,3rd}$$

Level-2 Model (annual data)

$$\beta_{0j,3rd} = \gamma_{00,3rd} + \gamma_{01,3rd}*(SMOKE_j) + u_{0j,3rd}$$

$$\beta_{1j,3rd} = \gamma_{10,3rd}$$

$$\beta_{2j,3rd} = \gamma_{20,3rd}$$

Mixed Model

$$NDSPM_{ij} = \gamma_{00,3rd} + \gamma_{01,3rd}*SMOKE_j + \gamma_{10,3rd}*NCSPM_{ij} + \gamma_{20,3rd}*PFVPH_{ij} + u_{0j,3rd} + r_{ij,3rd} \quad (3)$$

In the literature, the mediation effect is divided into full mediation and partial mediation. For confirming the full mediating effect of NCSPM, the estimated coefficients $\gamma_{01,1st}$ and $\gamma_{01,2nd}$ in model (1) and model (2) should be both significant. In the case that the estimated coefficients $\gamma_{01,3rd}$ is not significant, and that $\gamma_{10,3rd}$ is significant in model (3), partial mediation effect comes. Identifying partial mediation effect is similar to checking complete mediation effect. It is different that $\gamma_{01,3rd}$ is significant, and that the absolute value of $\gamma_{01,3rd}$ is smaller than $\gamma_{01,1st}$.

(2) The moderated effect tests

Testing the mediating effect of multi-level moderation includes 2 empirical models, as shown in model (4) and model (5). In model (4), this study adds random terms u_{1j} and u_{2j} to the estimated coefficients γ_{10} and γ_{20} of NCSPM and PFVPH in model (3) and tests whether the variance of u_{1j} and u_{2j} in model (4) is significantly different from 0.

Level-1 Model (daily data)

$$NDSPM_{ij} = \beta_{0j,4th} + \beta_{1j,4th}*(NCSPM_{ij}) + \beta_{2j,4th}*(PFVPH_{ij}) + r_{ij,4th}$$

Level-2 Model (annual data)

$\beta_{0j,4th} = \gamma_{00,4th} + \gamma_{01,4th}*(SMOKE_j) + u_{0j,4th}$

$\beta_{1j,4th} = \gamma_{10,4th} + u_{1j,4th}$

$\beta_{2j,4th} = \gamma_{20,4th} + u_{2j,4th}$

Mixed Model

$NDSPM_{ij} = \gamma_{00,4th} + \gamma_{01,4th}*SMOKE_j + \gamma_{10,4th}*NCSPM_{ij}$

$+ \gamma_{20,4th}*PFVPH_{ij} + u_{0j,4th} + u_{1j,4th}*NCSPM_{ij} + u_{2j,4th}*PFVPH_{ij} + r_{ij,4t}$ (4)

If variances of $u_{1j,4th}$ and $u_{2j,4th}$ in model (4) is significantly different from 0, $u_{1j,4th}$ and $u_{2j,4th}$ in model (4) can be substituted with SMOKE in model (5). The coefficients of SMOKE ($\gamma_{11,5th}$ and $\gamma_{21,5th}$) are moderating effects of SMOKE on NCSPM and PFVPH on NDSPM, respectively. Identifying the effect of $\gamma_{11,5th}$ and $\gamma_{21,5th}$ is important to check whether SMOKE has a moderating effect on NCSPM and PFVPH.

Level-1 Model (daily data)

$NDSPM_{ij} = \beta_{0j,5th} + \beta_{1j,5th}*(NCSPM_{ij}) + \beta_{2j,5th}*(PFVPH_{ij}) + r_{ij,5th}$

Level-2 Model (annual data)

$\beta_{0j,5th} = \gamma_{00,5th} + \gamma_{01,5th}*(SMOKE_j) + u_{0j,5th}$

$\beta_{1j,5th} = \gamma_{10,5th} + \gamma_{11,5th}*(SMOKE_j)$

$\beta_{2j,5th} = \gamma_{20,5th} + \gamma_{21,5th}*(SMOKE_j)$

Mixed Model

$NDSPM_{ij} = \gamma_{00,5th} + \gamma_{01,5th}*SMOKE_j + \gamma_{10,5th}*NCSPM_{ij} + \gamma_{11,5th}*SMOKE_j*NCSPM_{ij} + \gamma_{20,5th}$

$*PFVPH_{ij} + \gamma_{21,5th}*SMOKE_j*PFVPH_{ij} + u_{0j,5th} + r_{ij,5th}$ (5)

There are two types of HLM estimation methods: restricted maximum likelihood (RML) and full maximum likelihood (FML). The FML estimation method is relatively easy to calculate and identify estimates regression coefficients and overall chi-square values. In the meantime, RML only tests the variance component. This study compares deviance of two nested models in the future; the FML estimation method is employed.

Results

Descriptive Statistics

Table 1 shows the outcome of integrating daily data and annual data with the statistical software HLM version 8.1.

Table 1. Descriptive statistics of the data

Variables	Obs.	Mean	S.D.	Min	Max
New cases smoothed per million (NCSPM)	37,163	351.62	713.48	0	10,968.16
New deaths smoothed per million (NDSPM)	37,163	2.46	3.5	0	30.7
People fully vaccinated per hundred (PFVPH)	37,163	38.99	29.28	0	135.13
Smoking rate of a country (SMOKE)	327	20.82	9.11	3.78	43.9

Sources: Daily data from Our World in Data (2022) and annual data from World Bank (2022), author's own compilation.

Based on the Table 1, incomplete data was removed. There are 37,163 daily data in total. The averages of NCSPM, NDSPM and PFVPH are 351.62, 2.46 and 38.99. Standard deviations are 713.48, 3.5 and 29.28, respectively. Minimum values are all 0. Maximum values are 10,968.16, 30.7 and 135.13, respectively. There are 327 annual data on smoking rate. Mean, standard deviation, minimum value and maximum value are 20.82, 9.11, 3.78 and 43.9, respectively.

Model Simulations

This section presents results of the estimation and test of model 0 to 5 and analyzes their empirical implications. The first finding is the empirical results of model 0 in Table 2. The first row in Table 2 is the intercept term values of the three variables NDSPM, NCSPM and PFVPH, in order: 1.850; 329.955; and 35.021. The t-statistics standardized by robust standard errors are all significant at the 1% level of significance; and the variance values of the intercept terms are 4.273; 256, 481; and 733. Their χ^2 statistic values are all significant at the 1% level of significance. ICC values are 0.361, 0.449 and 0.693 respectively, and all are greater than 0.059 (Cohen, 1988). This indicates that the sample data is suitable for the analysis method of HLM.

Table 2. The empirical results of model 0

	model 0		
	NDSPM	NCSPM	PFVPH
INTERCEPT	1.850***	329.955***	35.021***
$(\widehat{\gamma_{00,null}})$	(0.118)	(28.687)	(1.511)
INTERCEPT $V(\widehat{u_{0j,null}})$	4.273	256,481	733

	model 0		
	NDSPM	NCSPM	PFVPH
level-1 $V(\widehat{r_{1j,null}})$	7.557	314,851	325
χ^2 $(\widehat{u_{0j,null}})$	25,222***	23,301***	63,087***
Deviance	181,781	577,210	321,969
ICC	0.361	0.449	0.693

Note: Arabic numbers in parentheses are robust standard deviations.

, ** and * = significant at 10%, 5% and 1%, respectively.*

The empirical results of model 1, 2, and 3 are collated in Table 3. To improve the interpretability of the intercept term, both the explanatory variable SMOKE and the control variable PFVPH are deducted from the total mean of each variable. Model 1 in Table 3 shows that the estimated value of the SMOKE variable is 0.113, which is significant at the 1% level of significance. When SMOKE increases by 1/100 people, the NDSPM will increase by 0.113/million people. The estimated value of the PFVPH variable is -0.032, which is also significant at the 1% significance level. As every 1/100 increase in PFVPH, the NDSPM will decrease by 0.032/million people. It shows the vaccine's epidemic prevention effect.

Model 2 in Table 3 shows that the estimated value of the SMOKE variable is 14.382, which is significant at the 1% level of significance. As SMOKE increases by 1/100 people, the NCSPM increases by 14.382/million people. The estimated value of the PFVPH variable is 0.578, which is not significant. It indicates that the vaccine's anti-epidemic effect on the infection of new coronary pneumonia is not significant. Model 3 in Table 3 shows that the estimated value of the SMOKE variable is 0.089, which is significant at the 1% significance level. As every 1/100 increases in SMOKE, the NDSPM increases by 0.089/million. The estimated value of the NCSPM variable is 0.002, which is significant at the 1% significance level. This means that as NCSPM increases by 1/million people, NDSPM increases by 0.002/million people. The estimated value of the PFVPH variable is -0.033, which is significant at 1% significant level. It means that as every 1/100 increases in PFVPH, the NDSPM decreases by 0.033/million people. It shows vaccine's anti-epidemic effect.

The empirical results of model 1, 2, and 3 show the multilevel mediation effect of newly COVID-19 cases. After adding new COVID-19 cases to model 3, the impact of smoking on new deaths decreased from 0.113 to 0.089. All are significant at the 1% significance level. It shows partial mediating effect of new COVID-19 cases.

Table 3. The test of mediation effect

model 1		model 2		model 3	
	NDSPM		NCSPM		NDSPM
INTERCEPT	1.732***	INTERCEPT	332.071***	INTERCEPT	1.764***
$(\widehat{\gamma_{00,1st}})$	(0.109)	$(\widehat{\gamma_{00,2nd}})$	(27.422)	$(\widehat{\gamma_{00,3rd}})$	(0.101)

model 1		model 2		model 3	
	NDSPM		NCSPM		NDSPM
SMOKE	0.113***	SMOKE	14.382***	SMOKE	0.089***
($\widehat{\gamma_{01,1st}}$)	(0.014)	($\widehat{\gamma_{01,2nd}}$)	(2.858)	($\widehat{\gamma_{01,3rd}}$)	(0.013)
				NCSPM	0.002***
				($\widehat{\gamma_{10,3rd}}$)	(0.0003)
PFVPH	-0.032***	PFVPH	0.578	PFVPH	-0.033***
($\widehat{\gamma_{10,1st}}$)	(0.007)	($\widehat{\gamma_{10,2nd}}$)	(0.495)	($\widehat{\gamma_{20,3rd}}$)	(0.007)
INTERCEPT V($\widehat{u_{0j,1st}}$)	3.926	INTERCEPT V($\widehat{u_{0j,2nd}}$)	230,814	INTERCEPT V($\widehat{u_{0j,3rd}}$)	3.301
level-1 V($\widehat{r_{ij,1st}}$)	7.203	level-1 V($\widehat{r_{ij,2nd}}$)	314,829	level-1 V($\widehat{r_{ij,3rd}}$)	6.330
χ^2 ($\widehat{u_{0j,1st}}$)	22,068***	χ^2 ($\widehat{u_{0j,2nd}}$)	21,610***	χ^2 ($\widehat{u_{0j,3rd}}$)	22,912***
Deviance	179,988	Deviance	577,175	Deviance	175,171

Note: Arabic numbers in parentheses are robust standard deviations.

, ** and * = significant at 10%, 5% and 1%, respectively.*

For a clearer and more intuitive visual effect, Figure 6 illustrates the empirical results of model 1 and 2 in Table 3. According to a single solid line, smoking significantly increases the number of deaths and vaccines reduce the risk of death. The new death cases are significantly associated with epidemic prevention effect. According to a double solid line, smoking significantly increases the number of confirmed cases and the vaccine has no significant epidemic prevention effect on the newly confirmed cases.

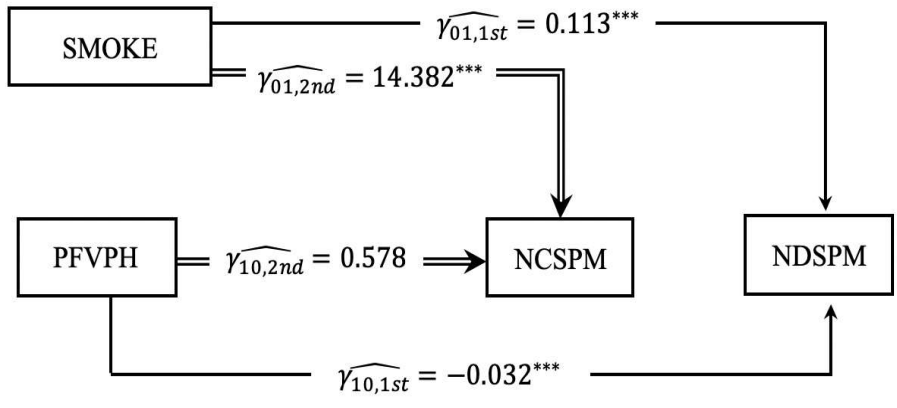


Figure 6. Visualization of model 1 and 2 of Table 3

Figure 7 shows the empirical results of model 3 in Table 3. After adding the mediating variable - newly

confirmed cases, the impact of smoking on new deaths decreases from 0.113 in Figure 6 to 0.089 in Figure 7. It is significant at the 1% significance level and proves partial mediating effect of newly confirmed cases.

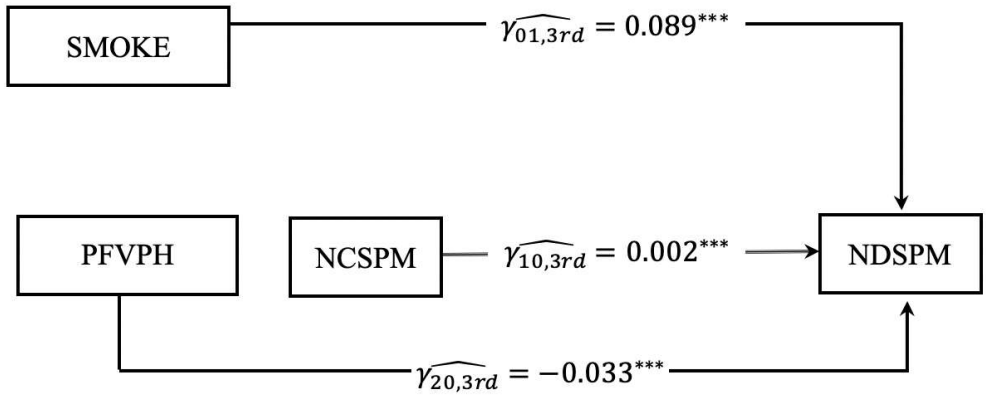


Figure 7. Visualization of model 3 of Table 3

The findings indicate that smoking has a significant positive impact on newly confirmed cases and deaths, and that there is a partial mediating effect of newly confirmed cases on new deaths (Kabbani & Olds, 2020; Heijink et al., 2021; Li et al., 2021). This study used multi-level moderated mediation (3M) model 4 and 5 to observe whether smoking moderates the effect of newly confirmed cases and complete vaccinations on new deaths. The empirical results are summarized in Table 4. It shows whether the impact of newly confirmed cases and the number of complete vaccinations on new deaths is fixed. The slope term of model 4 was added as a random variable. It was tested whether the variance of the random variable is significantly greater than 0. In Table 4, the variances of the slope terms of newly confirmed cases and complete vaccinations for new deaths are 0.00009 and 0.002, and the chi-square statistics (χ^2) are 13,534 and 7,838. It is significant at the 1% significance level. It indicates that there is a significant variation in the slope terms of newly confirmed cases and the number of complete vaccinations on new deaths.

In model 5, the smoking rate was added to the effects of newly diagnosed cases and the number of complete vaccinations on new deaths. The estimated coefficients are 0.00007 and 0.001 respectively. The smoking moderated effect for NCSPM to NDSPM is significant at the 10% significance level. But the moderated effect of smoking rates for the number of complete vaccinations on new deaths is not significant.

Table 4. The test of moderated effect

model 4		model 5	
	NDSPM		NDSPM
INTERCEPT	3.273***	INTERCEPT	1.635***
($\widehat{\gamma_{00,4th}}$)	(0.241)	($\widehat{\gamma_{00,5th}}$)	(0.113)
SMOKE	0.050***	SMOKE	0.103***
($\widehat{\gamma_{01,4th}}$)	(0.009)	($\widehat{\gamma_{01,5th}}$)	(0.017)

model 4		model 5	
	NDSPM		NDSPM
NCSPM	0.007***	NCSPM	0.001***
($\widehat{\gamma_{10,4th}}$)	(0.001)	($\widehat{\gamma_{10,5th}}$)	(0.0003)
		SMOKE	0.00007*
		($\widehat{\gamma_{11,5th}}$)	(0.00004)
PFVPH	-0.012*	PFVPH	-0.035***
($\widehat{\gamma_{20,4th}}$)	(0.003)	($\widehat{\gamma_{20,5th}}$)	(0.008)
		SMOKE	0.001
		($\widehat{\gamma_{21,5th}}$)	(0.001)
INTERCEPT V($\widehat{u_{0J,4th}}$)	11.890	INTERCEPT V($\widehat{u_{0J,5th}}$)	3.573
NCSPM V($\widehat{u_{1J,4th}}$)	0.00009		
PFVPH V($\widehat{u_{2J,4th}}$)	0.002		
level-1 V($\widehat{r_{IJ,4th}}$)	2.330	level-1 V($\widehat{r_{IJ,5th}}$)	6.243
χ^2		χ^2	
INTERCEPT ($\widehat{u_{0J,4th}}$)	18,919***	INTERCEPT ($\widehat{u_{0J,5th}}$)	24,548***
NCSPM ($\widehat{u_{1J,4th}}$)	13,534***		
PFVPH ($\widehat{u_{2J,4th}}$)	7,838***		
Deviance	139,857	Deviance	174,688

Note: Arabic numbers in parentheses are robust standard deviations.

*, ** and *** = significant at 10%, 5% and 1%, respectively.

Figure 8 illustrates the empirical results of model 5 in Table 4. Figure 8 shows that the smoking rate significantly increases the number of new deaths. Its estimated value ($\widehat{\gamma_{01,5th}}$) is 0.103, which is significant at the 1% significance level. The estimated coefficients ($\widehat{\gamma_{10,5th}}$ & $\widehat{\gamma_{20,5th}}$) of newly confirmed cases and the number of complete vaccinations on new deaths are 0.001 and -0.035, which are significant at the 1% level of significance. It shows that there is a cross-level partial intermediary effect in newly confirmed cases, and that vaccines have an epidemic prevention effect on new deaths. In terms of the adjustment effect of smoking rate, it shows that smoking rate significantly and positively moderates the effect of newly diagnosed cases on new deaths. The estimated value ($\widehat{\gamma_{11,5th}}$) is 0.00007. Smoking rate adjusted to complete vaccination. Smoking has no moderating effect for the number of vaccines on new deaths. The estimated value ($\widehat{\gamma_{21,5th}}$) is 0.001.

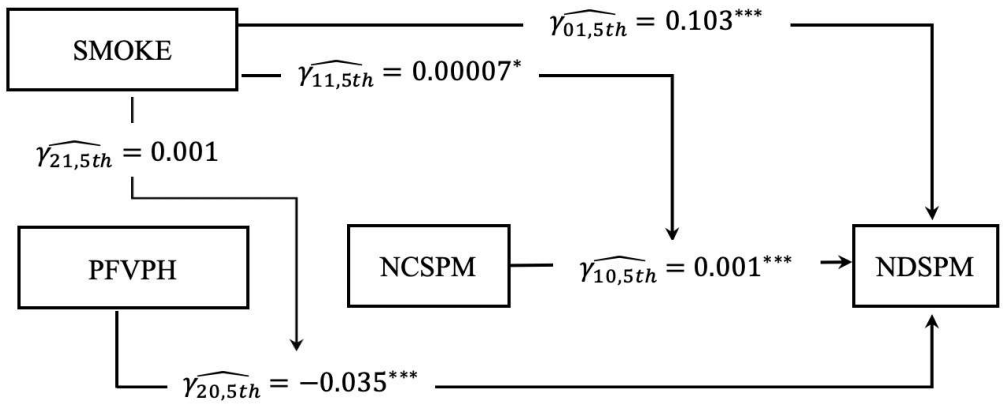


Figure 8. Visualization of model 4 and 5 of Table 4

Discussion

In order to understand the relationship between smoking and new coronary pneumonia, many researchers have conducted many studies (Cai, 2020; Smith *et al.*, 2020; Kabbani & Olds, 2020). They all believe that smoking is easy to worsen symptoms of new coronary pneumonia. However, some suggested that smoking may reduce symptoms of COVID-19 (Kloc et al., 2020; Tajlil et al., 2020; Tizabi et al., 2020). Given the divergence in the relationship between smoking and new coronary pneumonia, Gupta *et al.* (2021) stated that the relationship between smoking and new coronary pneumonia still cannot reach a definite conclusion. Edwards and Munafò (2020) highlighted that many studies about the relationship between smoking and new coronary pneumonia are at a very preliminary stage. Therefore, this study aimed to observe the relationship between smoking and new coronary pneumonia in a broader perspective. We collected data on new coronary pneumonia extensively and checked the number of vaccines provided in various countries to examine the relationship between smoking and various COVID-19 data.

According to the findings, as a country has a higher rate of smokers, it brings a higher contagion rate of COVID-19, and it leads to a high death rate. This result is in line with the previous studies. They claimed that smoking is significantly related to the progression of COVID-19 than never smoke. It turns out that smoking increases the severity of pulmonary infections from the damage of upper airways and the reduced the function of pulmonary immune (Patanavanich & Glantz, 2020). It also shows that smoking causes the risk of death among COVID-19 patients. Because smoking is able to impair lung immunity and promotes mucociliary-clearing dysfunction, it can worsen infection. Smoking affects redox balance and promotes the production of pro-inflammatory cytokines including interleukin-6 and interleukin-8. This process encourages cytokine storm. It leads to overproduction of similar inflammatory mediators and is strongly associated with

adverse outcomes among COVID-19 patients. Recent researches have proved that smoking increases ACE2 performance as a receptor as COVID-19 virus causes severe acute respiratory syndrome. Although the relationship between ACE2 performance and the severity of COVID-19 is yet unknown, it denotes that ACE2 elevation contributes to worsening prognoses from vascular dysfunction or a pro-inflammatory response among smokers (Hou *et al.*, 2021).

On the other hand, the findings are against some previous studies saying that smoking lowers COVID-19 contagion in comparison with non-smoking and former smoking. Severe COVID patients were not many in the previous studies. It suggested that evidence should be checked with caution. Even though there is a significant association between smoking and the progress of COVID-19, it cannot be regarded as an effective defense against infection. In the case group, a low number of smokers who contracted COVID-19 than in the control group. This situation misled some previous studies. And they asserted that smoking is a protective factor against the prevalence of COVID-19, and that nicotine is a potential preventive agent against COVID-19 infection (Heydari & Arfaeinia, 2021). Our study suggests that potential explanation over different results relates to the progress of COVID-19 disease and randomness in sample collection (Paleiron *et al.*, 2021). Our study addressed the relationship between new cases of smokers as well as the new death under COVID-19 vaccination. These inconsistent results stem from randomness among COVID-19 patients. The findings are also strengthened by our additional analysis. It shows the multilevel mediation effect of new COVID-19 cases in the relationship between smoking and new death of COVID-19. This study found the mediating effect of new case of COVID-19 between smoking and new death among COVID-19 patients. The findings are consistent with previous study saying that tobacco is linked to an elevated risk of infection in the respiratory tract. In the meantime, smoking also changes structure and function of the immune system. Macrophages, neutrophils, and inflammatory mediators are stimulated to produce innate immune cells as cigarette smoke comes for a short time. But prolonged exposure impairs that punction. Smoking impairs the T- and B-cell capabilities in the adaptive immune system and lowers antibody production (Brown, 2022). Smoking generally increases the risk of viral infection including COVID-19 infection in the upper respiratory tract, (Jiang *et al.*, 2020; Brown, 2022). Data shows that more than 6 million people have died worldwide from extremely contagious viral infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Such a pandemic has shown that COVID-19 has devastated numerous nations and wreaked healthcare systems (Cascella *et al.*, 2022). It is clear in the mediation model that smoking leads to new case of COVID-19, and that it in turn relates to the new death number of COVID-19.

We also proved that smoking rate significantly and positively moderates the effect of newly diagnosed cases on new deaths. Our results are in line with previous studies. That detrimental effects of tobacco on lung health, smoking has been proved to relates to illness. Smokers are more susceptible to infectious diseases because smoking weakens their immune systems. Thus, mortality in the smokers were checked because smoking has a greater impact on COVID-19 disease. Once a patient is diagnosed with COVID-19, it is crucial to put a lot of emphasis on quitting smoking. And it should be a priority to smokers with comorbidities (Heydari & Arfaeinia, 2021). Thus, the findings highlight that smoke moderates the increased

number of new deaths smoothed per million among new deaths smoothed per million.

Conclusion

The empirical results show that the smoking rate significantly increases the number of newly diagnosed and death cases. Smoking rate has a significantly positive influence on the impact of newly diagnosed cases on new deaths, but the smoking rate cannot moderate complete vaccination on the number of new deaths. The vaccination has a significant anti-epidemic effect on the number of new deaths, but it has no significant anti-epidemic effect on newly confirmed cases.

Smoking is classified into some categories (active smoker, passive smoker or exposure to second-hand smoker, former smoker, and non-smoker). Our current study did not control those classification as well as packyears in smoking. It could create a potential bias in overall estimation. Nonetheless, this study has some strengths. This study employed big data from 160 countries for January 1, 2020 through June 30, 2022. The data was analyzed by Hierarchical Linear Modeling (HLM). It allows of more accurate prediction. Our findings have a high generalizability around the world.

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