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LETTER TO THE EDITOR

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Risk and protective factors of SARS-CoV-2 infection

To the Editor,

It has been reported that coexistent chronic diseases are strongly associated with coronavirus disease-2019 (COVID-19) severity.[1] Investigations of predictors for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection itself, however, have been seldom performed. Although metaregression has been traditionally utilized to investigate heterogeneity in meta-analysis,[2] that considering a nation as a study in meta-analysis may be of use to screen potential risk and protective factors for SARS-CoV-2 infection. To screen the factors, metaregression of data from nations worldwide were herein conducted.

I extracted (a) total confirmed COVID-19 cases in 180 nations worldwide on 31 May 2020 from the World Health Organization (WHO, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/); (b) national total population in 2018, life expectancy at birth in 2016, medical-doctor and nursing/midwifery-personnel density in 2010 to 2018, hypertension prevalence in 2015, obesity prevalence in 2016, annual particulate matter 2.5 (PM2.5) concentrations in urban areas in 2016, population using safely managed drinking-water/sanitation services and hand-washing facility with soap/water in 2017, and daily ambient ultraviolet radiation in 1997 to 2003 from the WHO (https://www.who.int/gho/publications/world_health_statistics/2020/en/; https://apps.who.int/gho/data/node.main.122?lang=en); (c) population ages 0 to 14 and ≥65 in 2018, Gross Domestic Product and Gross National Income per capita, Purchasing Ppower Parity in 2016 to 2018 (mostly 2018), and diabetes prevalence in 2019 from the World Bank (https://data.worldbank.org/indicator/); (d) inbound tourism in 2014 to 2018 from the United Nations World Tourism Organization (https://www.e-unwto.org/doi/abs/10.5555/unwtotfb0000270020142018202001); and (e) bachelor's or equivalent (International Standard Classification of Education 6) in 2016 to 2018 from the United Nations Educational, Scientific and Cultural Organization (http://uis.unesco.org/en/topic/educational-attainment), all of which are listed in Table S1. Restricted maximum-likelihood metaregression in the random-effects model was performed using Comprehensive Meta-Analysis version 3 (Biostat, Englewood, NJ). To adjust for other covariates, we conducted the hierarchical multivariate models in addition to the univariate model.

Results of the metaregression are summarized in Table 1. A slope (coefficient) of the metaregression line for the COVID-19 prevalence in the multivariable models was significantly negative for population ages 0 to 14 (−0.0636; $P = .0021$; Figure 1A) and positive for obesity prevalence (0.0411; $P = .0099$; Figure 1B) and annual PM2.5 concentrations in urban areas (0.0158; $P = .0454$; Figure 1C), which would indicate that the COVID-19 prevalence decreases significantly as the proportion of children increases and that the COVID-19 prevalence increases significantly as the proportion of the obese and $PM_{2.5}$ increases.

The present metaregression to screen potential risk and protective factors suggests that children may be negatively and independently, and obesity/$PM_{2.5}$ may be positively and independently associated with SARS-CoV-2 infection. Our findings could be strengthened by low case fatality in children with COVID-19 (only one death in a total of 1124 cases)[3] and obesity predicting poor prognosis of COVID-19[4] demonstrated in recent systematic reviews. The present results, however, never denote directly that, for instance, the obese are at high risk for SARS-CoV-2 infection, which should be noted. Our findings demonstrate simply that the COVID-19 prevalence is higher in the nation where the obese are more. To determine whether, for instance, the obese are at high risk for SARS-CoV-2 infection, two approaches are considered. First, potential risk and protective factors could be investigated in a cohort including both COVID-19 patients and non-COVID-19 subjects (retrospective cohort study). It is never easy, however, to investigate the factors in the non-COVID-19 (healthy nonhospitalized) subjects. Second, the factors could be examined in both COVID-19 patients and control subjects (case-control study). In this occasion, however, the control subjects, who should be very comparable to the patients with COVID-19, must be strictly selected. Metaregression by use of "weighted" data from multiple clinical trials differs from simple regression by means of individual-patient data from a single study and accordingly can generate an equation of a "best-fit" regression line to express the relation between an outcome and a covariate.[5] Metaregression applied in the present study may be alternative to the above-mentioned approaches and could be of use at least to screen the factors.

In conclusion, children (negatively) and obesity/$PM_{2.5}$ (positively) may be independently associated with SARS-CoV-2 infection.

TABLE 1 Metaregression summary

Model, covariate	Coefficient	Lower limit of 95% CI	Upper limit of 95% CI	*P*	Figure
Univariable model I					
Age distribution					
[1] Population ages 0-14 (%)	−0.1136	−0.1360	−0.0913	<.0001*	
[2] Population ages ≥65 (%)	0.1521	0.1114	0.1928	<.0001*	
Economy					
[3] GDP per capita, PPP (current international $)	0.0001	0.0000	0.0001	<.0001*	
[4] GNI per capita, PPP (current international $)	0.0001	0.0001	0.0001	<.0001*	
Multivariable model I including all the above-mentioned covariates [1] to [4]					
[1] Population ages 0-14 (%)	−0.0636	−0.1038	−0.0234	.0021*	Figure 1A
[2] Population ages ≥65 (%)	−0.0163	−0.0738	0.0411	.5750	
[3] GDP per capita, PPP (current international $)	0.0000	−0.0000	0.0001	.8818	
[4] GNI per capita, PPP (current international $)	0.0000	−0.0000	0.0001	.1768	
Multivariable model II-1 adjusting for covariates [1] to [4]					
Public health					
[5] Life expectancy at birth (years)	0.0300	−0.0385	0.0984	.3885	
[6] Medical-doctor density (/10 000 population)	0.0292	0.0056	0.0529	.0156*	
[7] Nursing/midwifery-personnel density (/10 000 population)	0.0047	−0.0035	0.0130	.2604	
Multivariable model II-2 adjusting for covariates [1] to [4] and [8] to [10]					
[5] Life expectancy at birth (years)	0.0133	−0.0654	0.0919	.7396	
[6] Medical-doctor density (/10 000 population)	0.0158	−0.0085	0.0402	.2015	
[7] Nursing/midwifery-personnel density (/10 000 population)	0.0022	−0.0058	0.0103	.5844	
Multivariable model III adjusting for covariates [1] to [7]					
Disease					
[8] Hypertension prevalence (%)	−0.0086	−0.0790	0.0619	.8107	
[9] Obesity prevalence (%)	0.0411	0.0100	0.0722	.0099*	Figure 1B
[10] Diabetes prevalence (%)	−0.0261	−0.0935	0.0413	.4454	
Multivariable model IV adjusting for covariates [1] to [10]					
Environment					
[11] Annual PM2.5 concentrations in urban areas, μg/m^3	0.0158	0.0003	0.0313	.0454*	Figure 1C
[12] Daily ambient ultraviolet radiation, J/m^2	0.0001	−0.0002	0.0003	.6534	
Multivariable model V adjusting for covariates [1] to [12]					
Health infrastructure					
[13] Population using safely managed drinking-water services (%)	0.0171	−0.0044	0.0386	.1180	
[14] Population using safely managed sanitation services (%)	−0.0030	−0.0222	0.0161	.7521	
[15] Population using hand-washing facility with soap/water (%)	−0.0170	−0.0406	0.0065	.1525	
Miscellaneous					
[16] Inbound tourism (millions)	0.0027	−0.0056	0.0110	.5243	
[17] Bachelor's or equivalent (ISCED 6) (%)	−0.0029	−0.0485	0.0427	.9004	

Abbreviations: CI, confidence interval; GDP, gross domestic product; GNI, gross national income; ISCED, International Standard Classification of Education; $PM_{2.5}$, particulate matter 2.5; PPP, purchasing power parity.
*Statistically significant.

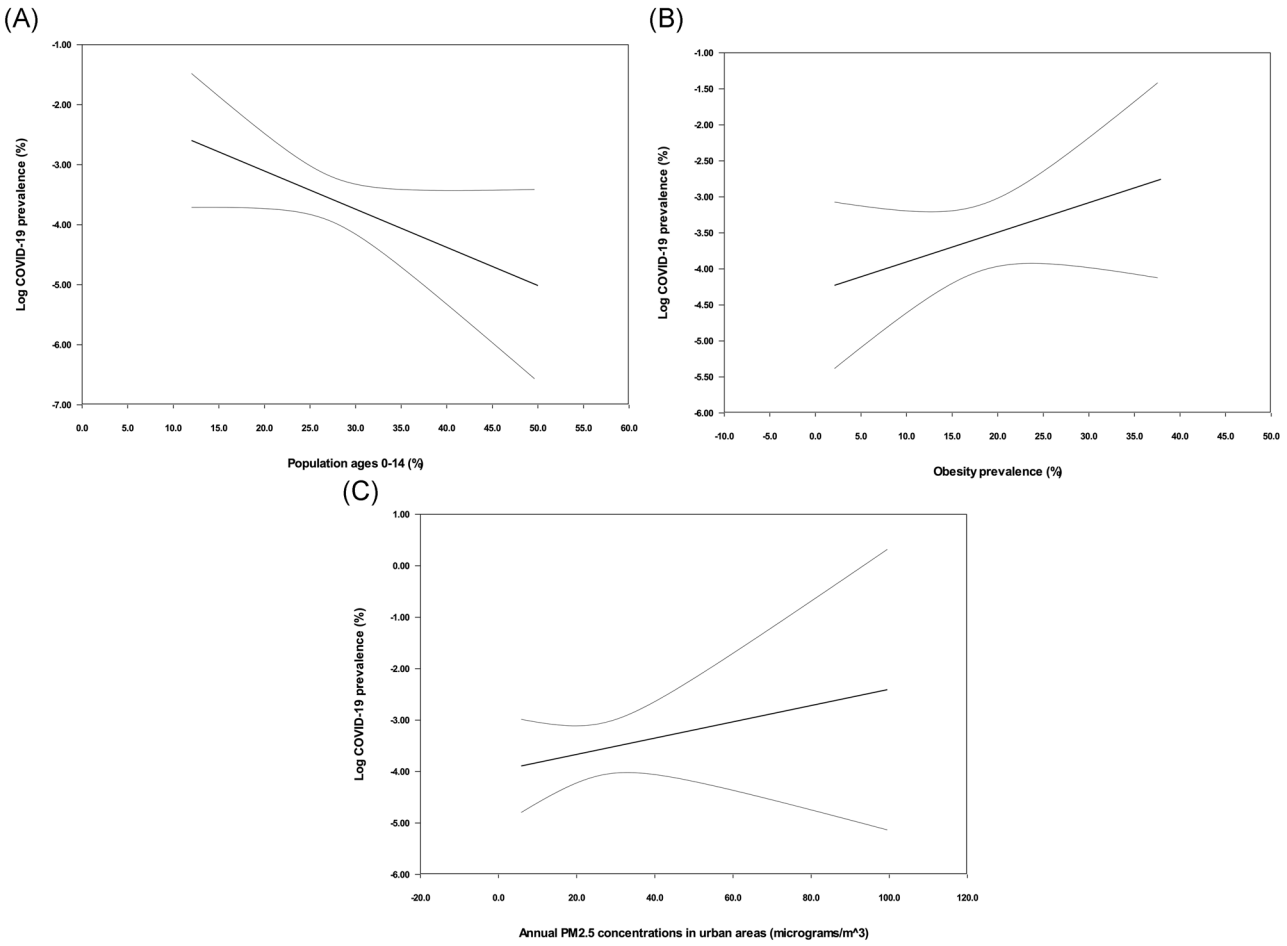

FIGURE 1 Metaregression lines with their 95% confidence interval curves depicting the coronavirus disease-2019 prevalence (plotted as the logarithm-transformed prevalence on the *y*-axis) as a function of a given covariate (plotted on the *x*-axis)

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.