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CE - LETTER TO THE EDITOR

# Systematic review of the prevalence of current smoking among hospitalized COVID-19 patients in China: could nicotine be a therapeutic option?

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Dear Editor,

We read with great interest the article by Farsalinos et al. [1] recently published in Internal and Emergency Medicine. The review [1] of 13 studies enrolling a total of 5960 hospitalized coronavirus disease 2019 (COVID-19) patients in China revealed unusually lower (approximately one-fourth) smoking prevalence in COVID-19 cases than that in the general population. Recent meta-analyses [2, 3], however, demonstrated that smoking was associated with worse prognosis and mortality in patients with COVID-19. To determine whether COVID-19 prevalence is modulated by smoking prevalence, meta-regression of Japanese prefectural data was herein conducted.

In each Japanese prefecture, the following was extracted: (1) number of confirmed COVID-19 cases on 15 June 2020 from the "Ministry of Health, Labour and Welfare" (https://www.mhlw.go.jp/content/10906000/000640393.pdf); (2) smoking prevalence (%) in 2016 (latest survey) from the "National Cancer Center Japan" (https://ganjoho.jp/reg_stat/statistics/dl/index.html#smoking); and (3-1) population per 1-km$^2$ inhabitable area (in 2018), (3-2) proportion (%) of males and < 15-year/≥ 65-year subjects (in 2018), (3-3) prevalence (/100 thousands) of neoplasm, type 2 diabetes mellitus, and essential hypertension (in 2017), (3-4) yearly average air temperature (°C), total sunshine hours (h), total precipitation (mm), and average relative humidity (%) (in 2018), (3-5) healthy life expectancy (years) (in 2016) and life expectancy at birth (years) (in 2015), (3-6) number (/100 thousands) of hospital beds (in 2017), doctors (in 2017), and nurses (in 2018), (3-7) monthly average households and persons assisted by livelihood protection (/1000 persons) (in 2017), and (3-8) monthly current income per household and living expenditure (≥ 2-person households–workers' households) (yen) (in 2018) from the "e-Stat, Statistics of Japan" (https://www.e-stat.go.jp) (Supplementary Table S1). To adjust for prefectural population density, COVID-19 prevalence was defined as the number of COVID-19 cases divided by the population per 100-km$^2$ inhabitable area. Univariable (including smoking prevalence as only a covariate) and multivariable (including all the above-mentioned parameters as covariates) random-effects meta-regression was performed using OpenMetaAnalyst (https://www.cebm.brown.edu/openmeta/index.html). A meta-regression graph depicted COVID-19 prevalence (plotted as logarithm-transformed prevalence on the Y-axis) as a function of smoking prevalence (plotted on the X-axis).

A slope of the univariable meta-regression line was significantly positive (coefficient, 0.319; 95% confidence interval [CI] 0.148–0.490; $p < 0.001$; Fig. 1), which indicated that COVID-19 prevalence increased significantly as smoking prevalence increased. The slope was also significantly positive (coefficient, 0.321; 95% CI 0.093–0.549; $p = 0.006$) even in multivariable meta-regression including all the 22 covariates together (Table 1).

The present meta-regression suggests a positive association of smoking prevalence with COVID-19 prevalence independent of various examined covariates. Remarkably lower current-smoking prevalence in hospitalized COVID-19 patients (6.5%; 95% CI 4.9–8.2%) than that in the general population (26.6%) in China (2018 Global Adult Tobacco Survey, https://www.who.int/docs/default-source/wpro--documents/countries/china/2018-gats-china-factsheet-cn-en.pdf?sfvrsn=3f4e2da9_2) has been reported in the article by Farsalinos et al. [1], which could be explained

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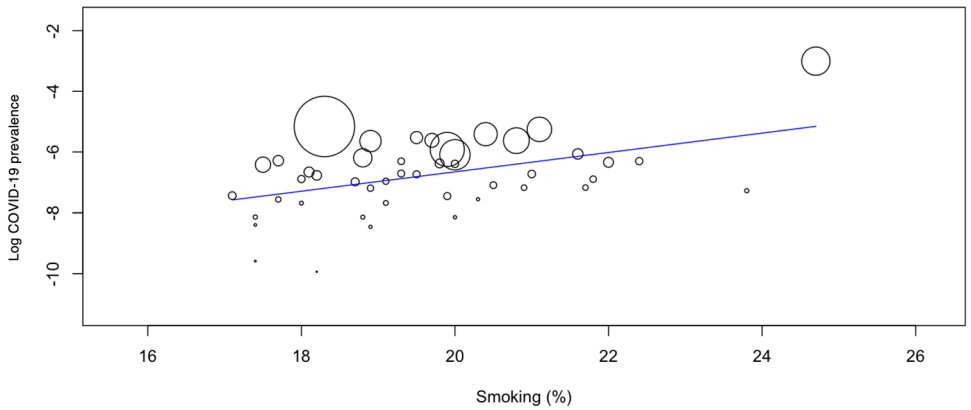


**Fig. 1** Meta-regression graph depicting COVID-19 prevalence (plotted as logarithm-transformed prevalence on the Y-axis) as a function of smoking prevalence (plotted on the X-axis)

**Table 1** Multivariable meta-regression summary

| Covariate | Coefficient | 95% confidence interval | | *p* value |
|---|---|---|---|---|
| | | Lower | Upper | |
| Smoking (%) | 0.321 | 0.093 | 0.549 | 0.006 |
| Male (%) | −0.323 | −0.892 | 0.247 | 0.267 |
| < 15 years (%) | −0.452 | −1.326 | 0.423 | 0.311 |
| ≥ 65 years (%) | −0.313 | −0.659 | 0.034 | 0.077 |
| Neoplasm (/100 thousands) | −0.000 | −0.000 | 0.000 | 0.577 |
| Type 2 diabetes mellitus (/100 thousands) | 0.007 | −0.002 | 0.015 | 0.116 |
| Essential hypertension (/100 thousands) | −0.009 | −0.021 | 0.003 | 0.136 |
| Yearly average air temperature (°C) | 0.146 | −0.166 | 0.457 | 0.359 |
| Yearly total sunshine hours (h) | −0.001 | −0.003 | 0.001 | 0.178 |
| Yearly total precipitation (mm) | 0.000 | −0.001 | 0.001 | 0.905 |
| Yearly average relative humidity (%) | −0.036 | −0.116 | 0.043 | 0.371 |
| Healthy life expectancy, male (years) | 0.077 | −0.537 | 0.692 | 0.805 |
| Healthy life expectancy, female (years) | 0.247 | −0.170 | 0.664 | 0.246 |
| Life expectancy at birth, male (years) | 0.652 | −0.567 | 1.870 | 0.294 |
| Life expectancy at birth, female (years) | −0.404 | −1.911 | 1.102 | 0.599 |
| Hospital beds (/100 thousands) | −0.001 | −0.003 | 0.002 | 0.708 |
| Doctors (/100 thousands) | −0.010 | −0.024 | 0.003 | 0.127 |
| Nurses (/100 thousands) | 0.003 | −0.003 | 0.010 | 0.354 |
| Monthly average households assisted by livelihood protection (/1000 households) | −0.206 | −0.440 | 0.028 | 0.085 |
| Monthly average persons assisted by livelihood protection (/1000 persons) | 0.379 | −0.003 | 0.762 | 0.294 |
| Monthly current income per household (yen) | 0.000 | −0.000 | 0.000 | 0.883 |
| Monthly living expenditure (yen) | 0.000 | −0.000 | 0.000 | 0.520 |

by nicotine-induced downregulation of the angiotensin converting enzyme 2 (ACE2) receptor [4], i.e. the receptor for severe acute respiratory syndrome coronavirus 2 causing COVID-19. This hypothesis, however, may be negated by the present findings of the positive association of smoking prevalence with COVID-19 prevalence in Japan. The interplay between smoking and COVID-19 may be exceedingly complicated and should not be oversimplified by the ACE2 hypothesis. Despite well documenting the smoking risk on health, tobacco/cigarette smoke (e.g. nicotine, carbon monoxide, and menthol) is experimentally known to positively modulate the immune system and may exert both harmful and beneficial influences [5]. The main limitations of the present analysis included relatively small number of COVID-19 cases in each prefecture and latest survey of smoking prevalence 4 years before the study period investigating COVID-19 prevalence in 2020. It should be noted that the present results do not denote directly that smokers are at high risk for COVID-19. The present findings demonstrate simply that the COVID-19 prevalence is higher in the

prefecture where smoking prevalence is higher. However, the present results could be strengthened and explained by the reported association of smoking with worse prognosis and mortality in COVID-19 patients [1, 2].

In conclusion, smoking may be independently associated with COVID-19, which should be confirmed by further experimental, clinical and epidemiological investigations.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Human and animal rights** Not applicable.

**Informed consent** Not applicable.

## References

1. Farsalinos K, Barbouni A, Niaura R (2020) Systematic review of the prevalence of current smoking among hospitalized COVID-19 patients in China: could nicotine be a therapeutic option? Intern Emerg Med. https://doi.org/10.1007/s11739-020-02355-7
2. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, Li Q, Jiang C, Zhou Y, Liu S, Ye C, Zhang P, Xing Y, Guo H, Tang W (2020) Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. J Infect. https://doi.org/10.1016/j.jinf.2020.04.021
3. Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Lian N, Deng Y, Lin S (2020) The impact of COPD and smoking history on the severity of Covid-19: a systemic review and meta-analysis. J Med Virol. https://doi.org/10.1002/jmv.25889
4. Oakes JM, Fuchs RM, Gardner JD, Lazartigues E, Yue X (2018) Nicotine and the renin-angiotensin system. Am J Physiol Regul Integr Comp Physiol 315:R895–R906
5. Polosa R, Caci G (2020) COVID-19: counter-intuitive data on smoking prevalence and therapeutic implications for nicotine. Intern Emerg Med. https://doi.org/10.1007/s11739-020-02361-9