# Smoking quantitatively increases risk for COVID-19



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*To the Editor*:

The coronavirus disease 2019 (COVID-19) pandemic has raised concern about the influence of smoking and alcohol drinking behaviour on the susceptibility to coronavirus infection and its severity. Widely debated, the connection remains highly controversial. Conclusions derived from observational studies commonly suffer from limited ability to discern causes and effects.

We used two-sample Mendelian randomisation (MR) to investigate individual causal relationships between multiple traits of smoking and alcohol intake and COVID-19 outcomes, and meta-analysis to evaluate overall causal effects of smoking or alcohol consumption on COVID-19 outcomes. We analysed summary results of genome-wide association studies, with seven datasets on smoking, including four quantitative datasets, providing the age of smoking (AOS; the age at which an individual started smoking cigarettes regularly, 341 427 participants) from Liu *et al.* [1], cigarettes per day from Liu *et al.* [1] (CPD1; 337 334 participants) and Erzurumluoglu *et al.* [2] (CPD2; 134 316 participants) [2], and cigarette pack-years (CPY, 622 409 participants) [2], and three datasets reporting the smoking status in binary form (regular smoker (current or former) *versus* participant who reported never being a regular smoker), namely, these by Liu *et al.* [1] (SMK1, 1 232 091 participants), Erzurumluoglu *et al.* [2] (SMK2, 353 630 participants), and Karlsson Linnér *et al.* [3] (SMK3, 518 633 participants). To analyse alcohol intake, three datasets were employed, including alcohol drinks per week from Liu *et al.* [1] (DPW1, 941 280 participants) and Karlsson Linnér *et al.* [3] (DPW2, 414 343 participants), and alcohol intake per day from Evangelou *et al.* [4] (DPD, 480 843 participants). For COVID-19, three datasets were obtained from the COVID-19 Host Genetic Initiative (round 4) [5], including three separate COVID-19 outcomes: severe COVID-19 (4438 very severe respiratory COVID-19 cases and 718 232 controls), COVID-19 hospitalisation (6406 hospitalised COVID-19 cases and 902 088 controls), and SARS-CoV-2 infection (14 134 cases with reported SARS-CoV-2 infection and 1 284 876 controls). The controls in the COVID-19 datasets were from genetically ancestry-matched samples without known SARS-CoV-2 infection. The participants of MR analysis should come from the same population across studies. All or a majority of the participants in the datasets were of European origins.

The main analyses were performed using the inverse-variance weighted (IVW) method and complemented with the weighted median and MR-Egger methods implemented in TwoSampleMR [6]. The intercept from the MR-Egger model was used as a measure of directional pleiotropy (a single-nucleotide polymorphism (SNP) influencing both the exposure and outcome through independent pathways). SNPs associated with smoking at genome-wide significance ($p<5\times10^{-8}$) were selected as instrumental variants and further pruned using a clumping $r^2$ cutoff of 0.01. The p-value threshold of $1\times10^{-5}$ was used for the CPY dataset due to the number of instrumental variants being less than five.

We performed meta-analyses for the causal effects in two quantitative smoking datasets (CPD1 and CPD2), three categorical smoking status datasets (SMK1, SMK2 and SMK3), and three alcohol drinking datasets on each of the three COVID-19 conditions, separately. A meta-analysis of the MR results was conducted using a random-effect model implemented in metafor [7].

As shown in figure 1a, our MR analysis detected eight causal associations between smoking traits and the COVID-19 outcomes: CPD1 (OR 2.69, 95% CI 1.27–5.67) and CPY (OR 1.87, 95% CI 1.15–3.02) with severe COVID-19; CPD1 (OR 1.92, 95% CI 1.04–3.55), CPY (OR 1.84, 95% CI 1.19–2.85), SMK1 (OR 2.46, 95% CI 1.22–4.98) and SMK2 (OR 2.49, 95% CI 1.23–5.04) with COVID-19 hospitalisation; SMK1 (OR 1.47, 95% CI 1.01–2.13 and SMK2 (OR 1.76, 95% CI 1.15–2.70) with SARS-CoV-2 infection.

Shareable abstract (@ERSpublications)
**A one standard deviation increase in cigarettes smoked per day is associated with 2.5-fold increased risk for very severe COVID-19 and 2-fold increased risk for hospitalisation with COVID-19**
https://bit.ly/2UuVO1o

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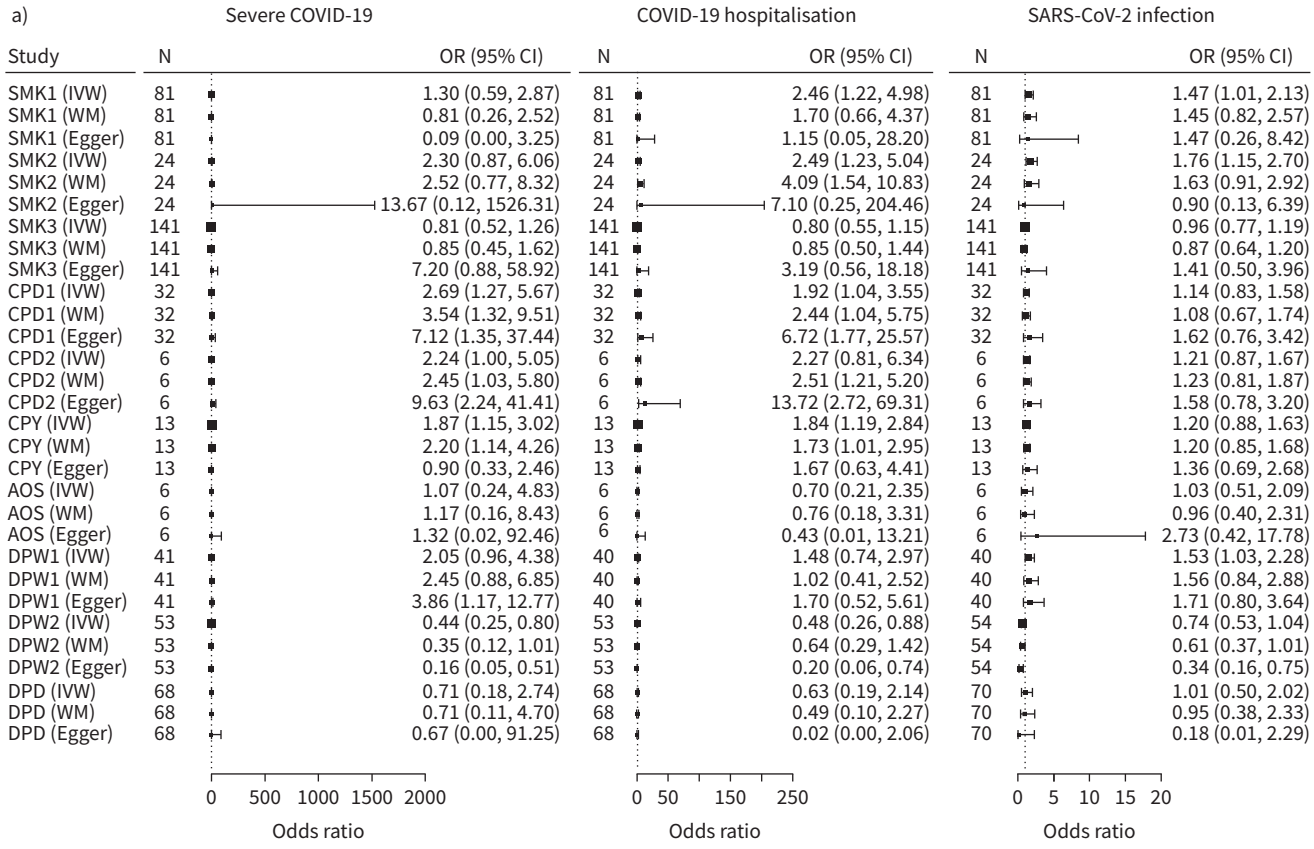
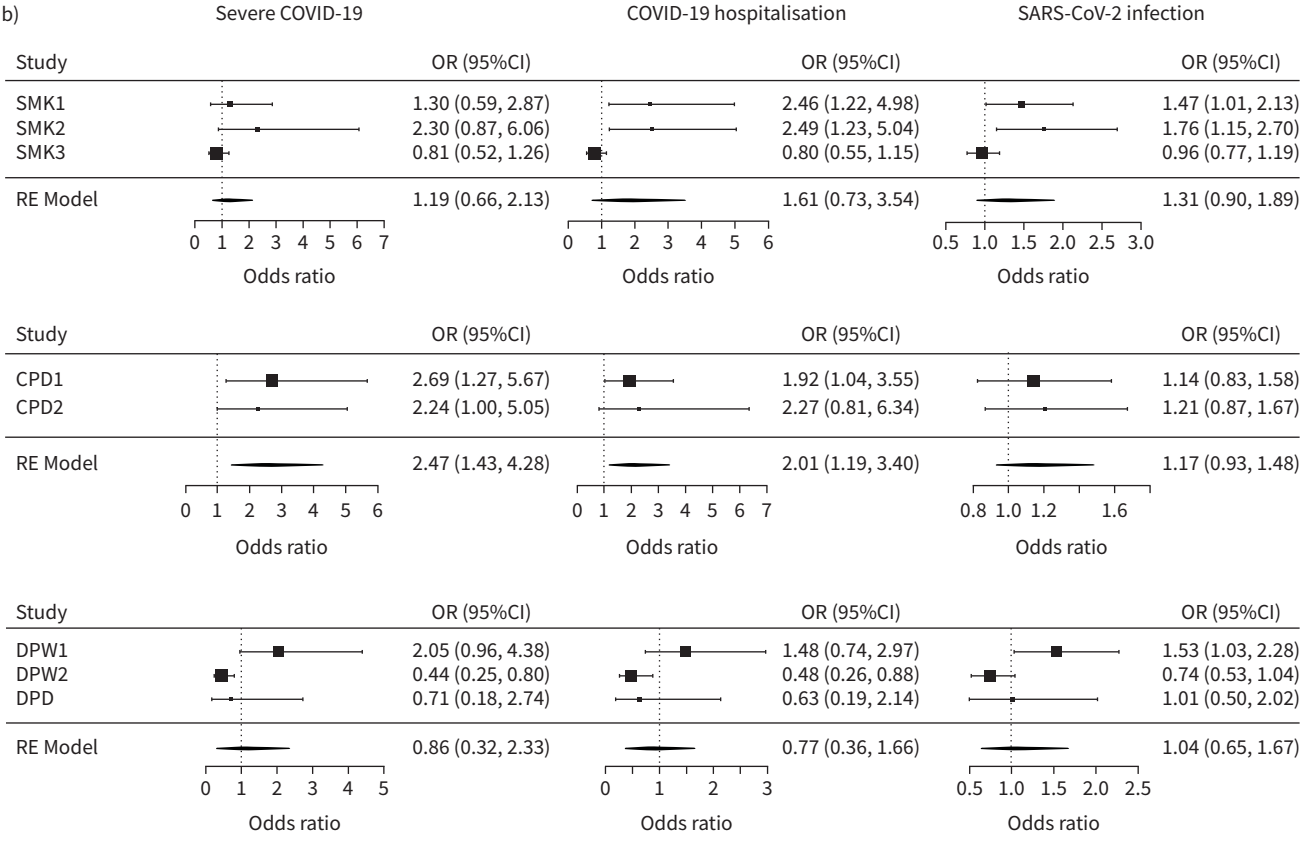
a)


Severe COVID-19
COVID-19 hospitalisation
SARS-CoV-2 infection
Study N OR (95% CI) N OR (95% CI) N OR (95% CI)
SMK1 (IVW) 81 1.30 (0.59, 2.87) 81 2.46 (1.22, 4.98) 81 1.47 (1.01, 2.13)
SMK1 (WM) 81 0.81 (0.26, 2.52) 81 1.70 (0.66, 4.37) 81 1.45 (0.82, 2.57)
SMK1 (Egger) 81 0.09 (0.00, 3.25) 81 1.15 (0.05, 28.20) 81 1.47 (0.26, 8.42)
SMK2 (IVW) 24 2.30 (0.87, 6.06) 24 2.49 (1.23, 5.04) 24 1.76 (1.15, 2.70)
SMK2 (WM) 24 2.52 (0.77, 8.32) 24 4.09 (1.54, 10.83) 24 1.63 (0.91, 2.92)
SMK2 (Egger) 24 13.67 (0.12, 1526.31) 24 7.10 (0.25, 204.46) 24 0.90 (0.13, 6.39)
SMK3 (IVW) 141 0.81 (0.52, 1.26) 141 0.80 (0.55, 1.15) 141 0.96 (0.77, 1.19)
SMK3 (WM) 141 0.85 (0.45, 1.62) 141 0.85 (0.50, 1.44) 141 0.87 (0.64, 1.20)
SMK3 (Egger) 141 7.20 (0.88, 58.92) 141 3.19 (0.56, 18.18) 141 1.41 (0.50, 3.96)
CPD1 (IVW) 32 2.69 (1.27, 5.67) 32 1.92 (1.04, 3.55) 32 1.14 (0.83, 1.58)
CPD1 (WM) 32 3.54 (1.32, 9.51) 32 2.44 (1.04, 5.75) 32 1.08 (0.67, 1.74)
CPD1 (Egger) 32 7.12 (1.35, 37.44) 32 6.72 (1.77, 25.57) 32 1.62 (0.76, 3.42)
CPD2 (IVW) 6 2.24 (1.00, 5.05) 6 2.27 (0.81, 6.34) 6 1.21 (0.87, 1.67)
CPD2 (WM) 6 2.45 (1.03, 5.80) 6 2.51 (1.21, 5.20) 6 1.23 (0.81, 1.87)
CPD2 (Egger) 6 9.63 (2.24, 41.41) 6 13.72 (2.72, 69.31) 6 1.58 (0.78, 3.20)
CPY (IVW) 13 1.87 (1.15, 3.02) 13 1.84 (1.19, 2.84) 13 1.20 (0.88, 1.63)
CPY (WM) 13 2.20 (1.14, 4.26) 13 1.73 (1.01, 2.95) 13 1.20 (0.85, 1.68)
CPY (Egger) 13 0.90 (0.33, 2.46) 13 1.67 (0.63, 4.41) 13 1.36 (0.69, 2.68)
AOS (IVW) 6 1.07 (0.24, 4.83) 6 0.70 (0.21, 2.35) 6 1.03 (0.51, 2.09)
AOS (WM) 6 1.17 (0.16, 8.43) 6 0.76 (0.18, 3.31) 6 0.96 (0.40, 2.31)
AOS (Egger) 6 1.32 (0.02, 92.46) 6 0.43 (0.01, 13.21) 6 2.73 (0.42, 17.78)
DPW1 (IVW) 41 2.05 (0.96, 4.38) 40 1.48 (0.74, 2.97) 40 1.53 (1.03, 2.28)
DPW1 (WM) 41 2.45 (0.88, 6.85) 40 1.02 (0.41, 2.52) 40 1.56 (0.84, 2.88)
DPW1 (Egger) 41 3.86 (1.17, 12.77) 40 1.70 (0.52, 5.61) 40 1.71 (0.80, 3.64)
DPW2 (IVW) 53 0.44 (0.25, 0.80) 53 0.48 (0.26, 0.88) 54 0.74 (0.53, 1.04)
DPW2 (WM) 53 0.35 (0.12, 1.01) 53 0.64 (0.29, 1.42) 54 0.61 (0.37, 1.01)
DPW2 (Egger) 53 0.16 (0.05, 0.51) 53 0.20 (0.06, 0.74) 54 0.34 (0.16, 0.75)
DPD (IVW) 68 0.71 (0.18, 2.74) 68 0.63 (0.19, 2.14) 70 1.01 (0.50, 2.02)
DPD (WM) 68 0.71 (0.11, 4.70) 68 0.49 (0.10, 2.27) 70 0.95 (0.38, 2.33)
DPD (Egger) 68 0.67 (0.00, 91.25) 68 0.02 (0.00, 2.06) 70 0.18 (0.01, 2.29)
0 500 1000 1500 2000
0 50 150 250
0 5 10 15 20
Odds ratio
Odds ratio
Odds ratio

b)


Severe COVID-19
COVID-19 hospitalisation
SARS-CoV-2 infection
Study OR (95%CI) OR (95%CI) OR (95%CI)
SMK1 1.30 (0.59, 2.87) 2.46 (1.22, 4.98) 1.47 (1.01, 2.13)
SMK2 2.30 (0.87, 6.06) 2.49 (1.23, 5.04) 1.76 (1.15, 2.70)
SMK3 0.81 (0.52, 1.26) 0.80 (0.55, 1.15) 0.96 (0.77, 1.19)
RE Model 1.19 (0.66, 2.13) 1.61 (0.73, 3.54) 1.31 (0.90, 1.89)
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0 1 2 3 4 5 6
0.5 1.0 1.5 2.0 2.5 3.0
Odds ratio
Odds ratio
Odds ratio
Study OR (95%CI) OR (95%CI) OR (95%CI)
CPD1 2.69 (1.27, 5.67) 1.92 (1.04, 3.55) 1.14 (0.83, 1.58)
CPD2 2.24 (1.00, 5.05) 2.27 (0.81, 6.34) 1.21 (0.87, 1.67)
RE Model 2.47 (1.43, 4.28) 2.01 (1.19, 3.40) 1.17 (0.93, 1.48)
0 1 2 3 4 5 6
0 1 2 3 4 5 6 7
0.8 1.0 1.2 1.6
Odds ratio
Odds ratio
Odds ratio
Study OR (95%CI) OR (95%CI) OR (95%CI)
DPW1 2.05 (0.96, 4.38) 1.48 (0.74, 2.97) 1.53 (1.03, 2.28)
DPW2 0.44 (0.25, 0.80) 0.48 (0.26, 0.88) 0.74 (0.53, 1.04)
DPD 0.71 (0.18, 2.74) 0.63 (0.19, 2.14) 1.01 (0.50, 2.02)
RE Model 0.86 (0.32, 2.33) 0.77 (0.36, 1.66) 1.04 (0.65, 1.67)
0 1 2 3 4 5
0 1 2 3
0.5 1.0 1.5 2.0 2.5
Odds ratio
Odds ratio
Odds ratio

**FIGURE 1** Causal associations between coronavirus disease 2019 (COVID-19) and smoking and alcohol drinking. CPD1: cigarettes per day from Liu *et al*. [1]; CPD2: cigarettes per day from Erzurumluoglu *et al*. [2]; CPY: cigarette pack-years from Erzurumluoglu *et al*. [2]; AOS: the age at which an individual started smoking cigarettes regularly from Liu *et al*. [1]; SMK1: smoking from Liu *et al*. [1]; SMK2: smoking from Erzurumluoglu *et al*. [2]; SMK3: smoking from Karlsson Linnér *et al*. [3]; DPW1: alcohol drinks per week from Liu *et al*. [1]; DPW2: alcohol drinks per week from Karlsson Linnér *et al*. [3]; DPD: alcohol drinking per day from Evangelou *et al*. [4]; IVW: inverse variance weighted; WM: weighted mean; Egger: MR Egger; RE: random effects. a) Mendelian randomisation analysis. Rows are exposures with different methods and columns are outcomes. b) Meta-analysis of the causal effects from IVW model. Rows are exposures with different methods and columns are outcomes.

Smoking status displayed mixed associations with COVID-19 outcomes, with smoking-related features in SMK1 and SMK2 tending to increase the risk for COVID-19 hospitalisation and in SMK3 tending to decrease this risk.

For alcohol traits, our MR analysis across the three alcohol datasets yielded inconsistent results. Within the Karlsson Linnér *et al*. [3] dataset (DPW2), alcohol consumption has shown a protective effect both on severe COVID-19 (OR 0.44, 95% CI 0.25–0.80) and COVID-19 hospitalisation (OR 0.48, 95% CI 0.26–0.88), while the analysis of the Liu *et al*. [1] dataset (DPW1) indicated that consumption of alcohol may increase risk for COVID-19 susceptibility (OR 1.53, 95% CI 1.03–2.28). No causal effects were detected when the Evangelou *et al*. [4] dataset was analysed.

The sensitivity analyses suggested that directions of causal effect estimates across the methods were predominantly consistent (figure 1a). Tests of MR-Egger regression intercepts did not support the directional pleiotropy of the genetic instrumental variables.

Our meta-analysis indicated that incremental increases in smoking intensity are positively associated with increased risk for severe COVID-19 (OR 2.47, 95% CI 1.43–4.28; $p=1.26\times10^{-3}$) and hospitalised COVID-19 (OR 2.01, 95% CI 1.19–3.40; $p=9.56\times10^{-3}$), while the binary smoking status and all the alcohol drinking traits had no associations with any kind of COVID-19 outcomes (figure 1b).

Our study reveals that the amount of smoking causally and positively influences the risk of COVID-19 severity, presumably due to reduced lung function caused by smoking of the tobacco, which is proportional to cigarette pack-years. However, the binary defined smoking status does not show any effect on susceptibility to COVID-19 or its severity. This inconsistency may reflect a balanced effect of possible protective effects of cigarette smoking as such, including intermittent ones, on susceptibility to COVID-19 and the extent of smoking-related lung damage which is evident in heavy smokers. Our study suggests that heavy smokers have an increased risk for the development of severe outcomes after SARS-CoV-2 infection. For heavy smokers, attention should be paid to avoidance of contact with the virus.

Our study reveals that the individual effects of alcohol consumption on COVID-19 susceptibility and severity are mixed, and may be cohort-specific. It is possible that in certain populations, the immunosuppressive effect of alcohol [8] may provide some protection, while in others, alcohol-related toxicity may outweigh this putative benefit. Overall, our study did not support a causal effect of alcohol consumption on COVID-19.

Several limitations are also to be acknowledged. Pleiotropy is a potential source of bias capable of threatening the validity of any MR study. However, our results were consistent in all analyses when performed by different MR methods, with no statistical indications of directional pleiotropy revealed in the case of smoking and COVID-19 connections.

In conclusion, our study indicated that a one standard deviation increase in cigarettes smoked per day is associated with 2.5-fold increased risk for severe COVID-19 and 2-fold increased risk for hospitalised COVID-19, while the smoking status and alcohol drinking traits have no associations with any kind of COVID-19 outcomes.

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Author contributions: F. Zhang conceived the study and performed the analyses; F. Zhang and A. Baranova drafted the manuscript. Both authors assisted with interpretation, commented on drafts of the manuscript. Both authors approved the final version.

Conflict of interest: F. Zhang has nothing to disclose. A. Baranova has nothing to disclose.

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