

Associated risks of smoking and possible benefits of cessation in Covid-19: a rapid narrative review

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Hernández-Pérez A, García-Gómez L, Rodríguez-Llamazares S, Thirión-Romero I, Osio-Echánove J, Pérez-Padilla R. Riesgos asociados con tabaquismo y posibles beneficios de cesación en Covid-19: una revisión narrativa rápida. *Salud Publica Mex.* 2021;63:262-267. <https://doi.org/10.21149/9371>

Abstract

Objective. To describe the possible risks associated to smoking in the spread and complications of Covid-19, emphasizing in the benefits of quitting smoking. **Materials and methods.** The narrative review methodology and the established process for Cochrane rapid reviews were used. **Results.** The scientific evidence related to smoking and Covid-19 remains limited. However, there is an already documented trend in cross-sectional, clinical studies and meta-analyses on the increased risk of adverse outcomes with Covid-19 associated with tobacco use. **Conclusions.** It is necessary to issue a warning that persons who smoke would have greater risks in the Covid-19 pandemic, which add to the many already known risks of tobacco use. Thus, quitting smoking becomes a relevant preventive measure to better confront SARS-CoV-2.

Keywords: smoking; coronavirus; Covid-19; SARS-CoV-2; review

Resumen

Objetivo. Describir los posibles riesgos asociados de tabaquismo con contagio y complicaciones por Covid-19, haciendo hincapié en los beneficios de dejar de fumar. **Material y métodos.** Se utilizó la metodología de revisión narrativa y el proceso establecido para las revisiones rápidas Cochrane. **Resultados.** La evidencia científica relacionada con el tabaquismo y Covid-19 todavía es limitada. Existe una tendencia ya documentada en estudios clínicos transversales y metaanálisis del aumento del riesgo de resultados adversos para Covid-19 asociados con el consumo de tabaco. **Conclusiones.** Es necesario advertir que las personas que fuman tendrán mayores riesgos en la pandemia de Covid-19, los cuales se suman a los muchos ya conocidos del consumo de tabaco, de modo que dejar de fumar se convierte en una medida preventiva relevante para enfrentar mejor el SARS-CoV-2.

Palabras clave: fumar; coronavirus; Covid-19; SARS-CoV-2; revisión

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After the outbreak of the Severe Acute Respiratory Syndrome Coronavirus infection (SARS-CoV-2) and the new Coronavirus disease (Covid-19) occurred in Wuhan, a city in the province of Hubei, China, a rapid community spread at the regional and international level was registered. With an exponential increase in the number of cases and deaths, it was declared a pandemic by the World Health Organization (WHO).¹ Globally, at June 30, 2020, there have been 10 185 374 confirmed cases of Covid-19, including 503 862 deaths, reported to WHO.² Additionally, hypertension, diabetes, obesity, smoking, and chronic obstructive pulmonary disease (COPD) have been reported as the main comorbidities associated with disease mortality.³⁻⁵

Smoking, in itself, is a global public health problem, according to the WHO World Report on trends in the prevalence of tobacco use between 2000 and 2025, and in 2018, there were 1.337 billion smokers. More than 8 million persons die due to tobacco use each year; tobacco kills one half of its users.⁶ At the same time, it is associated with one of every six deaths from non-communicable diseases that,⁷ as previously mentioned, have been identified as risk factors for death by Covid-19. Therefore, it is relevant to establish the risks associated with tobacco smoking in the midst of the pandemic, both for its infection rates and complications, while analyzing the potential benefits of smoking cessation as a health measure. This review briefly addresses the scientific evidence available to date, aiming to understand the risks of smoking associated with Covid-19, as well as emphasizing the importance of tobacco-related cessation measures, which can improve health conditions in the overall population.

Materials and methods

The narrative rapid review methodology was implemented with processes suggested for the Cochrane rapid reviews.⁸ A systematic search was conducted in May 2020 with no language restrictions under the following criteria: [smoking tobacco-SARS-CoV-2], [tobacco-Covid-19], and [smoking cessation-Covid-19] to identify manuscripts related to the objective. The search strategies were performed through four international databases (PubMed, SciELO, Scopus, and Google Scholar). In addition, extra searches with specific search algorithms for each section were performed in the reference lists of included studies to avoid missing papers. Additionally, WHO reports and one report of the Surgeon General on Tobacco were included. Titles and abstracts were reviewed by an emeritus researcher, a physician specializing in pulmonology and smoking. The full-text review was divided among the remainder researchers, and results were synthesized in narrative fashion.

Results

Pathophysiological interactions between smoking and coronavirus

Smoking is causal or contributes significantly to several chronic diseases, associated with adverse outcomes of Covid-19; including COPD; several types of cancer; atherosclerosis; coronary heart disease and cerebrovascular diseases; diabetes; obesity, and autoimmune diseases (table I). Smoking is also an activity that requires hand-face interactions, one of the main contagion pathways for Covid-19.⁹

Smoking also deteriorates varied defense mechanisms against respiratory pathogens,¹⁰ including mucociliary escalation, epithelial integrity, macrophage function, and other mechanisms involved in innate immunity.¹¹ The risk for pneumococcal, legionella, and mycoplasma pneumonia infection is about 3-5-times higher in smokers,¹² but also the risk for viral infections of the respiratory tract, such as respiratory syncytial virus,¹³ and influenza, and smokers have 34% more risk of acquiring the infection than nonsmokers.¹⁴

Smoking has also been found a risk for Acute Respiratory Distress Syndrome (ARDS) under several circumstances, probably due to the effects of smoke in the permeability of capillary and alveolar cells. Table I depicts several effects of tobacco that are likely relevant for Covid-19. Smoking had been considered an inflammatory disease that could facilitate the hyperinflammation produced by the Covid-19 in a group of patients with severe disease.

An interesting discussion developed on the relationship of nicotine and smoking with the Angiotensin-Converting Enzyme-2 receptor (ACE2), the target receptor for both SARS-CoV, the human respiratory coronavirus NL63, and especially SARS-CoV-2, the latter with greater affinity for the receptors.¹⁵ ACE2 was reported upregulated in the airway epithelium of smokers and possibly as acting as a new viral adhesion molecule, further indicating that smokers may be more susceptible to SARS-CoV-2 infection and may possibly develop Covid-19. Moreover, ACE2 is a critical mediator of renin-angiotensin system (RAS) signaling throughout the body, but particularly in heart, kidney, and gastrointestinal tract that, in addition to the lung, are additional known sites for SARS-CoV infection.¹⁵ Furthermore, ACE2 epithelial expression in lung cells obtained by bronchoscopy was increased in smokers compared with nonsmokers, while former smokers have an intermediate level of expression between these two groups.¹⁶ In smokers with COPD, the expression of ACE2 receptors in lung tissue was increased to a greater

degree than in smokers with normal lung function, and in these, more than in non-smokers.¹⁷ Something similar was found in the Middle East Respiratory Syndrome (MERS) infection, as its receptor (DPP4) mRNA and protein expressions were significantly higher in smokers compared with never smokers without airflow limitation and are inversely correlated with lung function.⁹

However, patients on ACE Inhibitors (ACEI) and Angiotensin 2 Receptor Blockers (ARB) do not appear to be at increased risk of infection or death.¹² Additionally, the role of ACE-2 receptors must continue to be considered uncertain and controversial.

Smoking history and risk of Covid-2019

WHO experts¹⁸ considered that smokers are more likely to develop severe disease with Covid-19, compared to non-smokers. The association of tobacco smoking and Covid-19 had been suspected since the publication of the first clinical case-series reports from Wuhan,^{5,19} where male populations were predominantly affected by Covid-19 compared to female populations.²⁰ In relatively small clinical studies, smoking in patients with Covid-19-induced pneumonia was significantly associated

with disease progression (N= 78; OR=12.187; 95%CI: 1.762-84.306; $p=0.011$),²¹ and was an independent risk factor associated with disease exacerbation after treatment (N= 95; OR= 16.13; $p=0.032$).²²

A systematic review with five studies and a total population of 1 549 patients²³ determined that smokers were 1.4 times more likely (RR= 1.4; 95%CI: 0.98-2.00) to have severe symptoms of Covid-19 and were approximately 2.4 times more likely to be admitted to an Intensive Care Unit (ICU), need mechanical ventilation, or die, when compared with non-smokers (RR= 2.4; 95%CI: 1.43-4.04). One initial meta-analysis found no association between smoking and Covid-19 disease,²⁴ but others found smoking associated with worse outcomes or death, as shown in table II,²⁴⁻²⁸ despite limitations likely including smoking-status misclassification and a tendency to decrease smoking with age, whereas there was the opposite tendency of Covid-19 lethality and the possible impact of pulmonary-inhaled treatment on Covid-19 outcomes.²⁹

The four main tobacco-related diseases are risk factors for Covid-19 complications or death: Chronic Obstructive Pulmonary Disease (COPD) (HR= 2.7; 95%CI: 1.4-5.0); diabetes (HR= 1.6; 95%CI: 1.03-2.5); hy-

Table I
RESUME OF EFFECTS OF TOBACCO SMOKING LIKELY RELEVANT FOR COVID-19

1. Development of comorbidities increasing the risk of adverse outcomes in Covid-19	Cardiovascular diseases: coronary heart disease, peripheral arterial disease, acute myocarditis, heart failure, atherosclerosis acceleration, promotion of thrombosis. Cerebrovascular diseases: Diabetes and lipid metabolism dysregulation. Obesity. COPD and asthma. Variety of cancers. Autoimmune diseases often requiring immunosuppressive therapy: RA, SLE, Crohn's disease. Renal disease.
2. Impairment of defense mechanisms	Innate immunity: injury to the respiratory epithelium, to mucociliary escalator; lower function of cells involved including macrophages, dendritic cells, NK cells, polymorphonuclear cells. Adaptive immunity: reduction in Immunoglobulins except for IgE, reduction in response to antigens and the association with pathogenic autoantibodies. Infections: increased risk for respiratory viral infection (influenza, rhinovirus), pneumococcal disease, tuberculosis. Microbiome modification. Chronic systemic inflammatory response: higher levels of leukocytes, c-reactive protein, interleukin-6, fibrinogen.
3. Increase of the risk of ARDS (under several circumstances)	Increase permeability of alveolar and capillary barrier. Lower production of surfactant. Increase in oxidative stress. Reduced immunity to infection. Change in microbiome. Chronic systemic inflammatory response.
4. Behaviors related to smoking	Sharing contaminated cigarettes, e-cigarettes, water pipes (hookah).

RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; NK cells: natural killer cells; IgE: allergen-specific immunoglobulin E; COPD: obstructive pulmonary disease

Table II
SUMMARY OF PUBLICATIONS ON THE ASSOCIATION BETWEEN SMOKING AND COVID-19

Study	Country/date	Exposure and outcome measures	Odds ratio (OR)-risk ratio (RR)	Other factors found
Lippi et al. 2020 ²⁴	Verona, Italy / March 9, 2020.	Smoking associated with disease severity	OR: 1.69 (95%CI: 0.41-6.92).	Trend towards higher risk was appreciable, no significant association, nor could one be found between active smoking and disease severity.
Zheng et al. 2020 ²⁵	Zhejiang, China / March 20, 2020.	Current smoking associated with disease progression	OR: 2.51 (95%CI: 1.39-3.32).	Male, aged more than 65 years, and smoking were risk factors for disease progression. Comorbidities such as hypertension, diabetes, cardiovascular disease, or respiratory diseases could also greatly affect the disease prognosis.
Patanavanich et al. 2020 ²⁶	San Francisco, United States / April 28, 2020.	Smoking behavior associated with disease progression	OR: 2.25 (95%CI: 1.49-3.39).	Limitations in the 12 papers included suggest that the actual risk of smoking may be higher.
Alqahtani et al. 2020 ²⁷	London, United Kingdom / March 24, 2020.	Smoking status associated with disease severity and mortality	RR: 1.45 (95%CI: 1.03-2.04).	22.30% of current smokers and 46% of ex-smokers had severe complications. A higher mortality rate of 38.5% was also observed among current smokers.
Zhao et al. 2020 ²⁸	Fujian, China / March 22, 2020.	Ongoing smoking associated with disease severity	OR: 1.98 (95%CI: 1.29-3.05).	The presence of COPD is associated with nearly a 4-fold higher risk of developing severe Covid-19 (OR= 4.38; 95%CI: 2.34-8.20).

COPD: Obstructive pulmonary disease

pertension (HR= 1.6; 95%CI: 1.07-2.3), and malignancy (HR= 3.5; 95%CI: 1.6-7.6).³⁰ Furthermore, having one comorbidity increases the probability of a complication or death outcome in Covid-19, while having two or more comorbidities doubles this probability.³⁰

A study from the United Kingdom reports an increased risk for death in current smokers compared with never smokers of 1.25 (95%CI: 1.12-1.40) when adjusting for age and sex; the latter disappears when the increased risk for death is fully adjusted, revealing 0.88 (95%CI: 0.79-0.99).¹² Proper adjustment for confounders, such as hypertension, diabetes, obesity, race, sex, and COPD, shows that all of these might be associated with tobacco smoking, and poor outcomes require larger samples.

Potential benefits of cessation during the health contingency

Although we were unable to find a study dealing with the benefit of quitting smoking during the epidemiological phenomenon of the Covid-19 pandemic, it is likely that this study would find a rapid improvement of Covid-19 outcomes, on solely observing the perioperative adverse outcomes of current smokers and how soon they improve after quitting smoking. Current smokers, 30 days after a noncardiac surgery, were more likely to die than never smokers (OR= 1.38; 95%CI: 1.11-1.72), to have pneumonia (OR= 2.09; 95%CI: 1.80-2.43), unplanned intubation (OR= 1.87; 95%CI: 1.58-2.21), or mechanical

ventilation (OR= 1.53; 95%CI: 1.31-1.79). In contrast, smokers who quit more than four weeks before surgery had lower risks of respiratory complications than current smokers (RR= 0.77; 95%CI: 0.61-0.96).³¹

At any age, smoking cessation reduces the risk of premature death, leads to rapid improvement in the level of high-density lipoprotein cholesterol, and remains the only established intervention to reduce loss of lung function over time among persons with COPD³² while reducing the risk of developing COPD in cigarette smokers.³³ Smoking cessation reduces the levels of inflammation markers³⁴ and hypercoagulability, allowing us to think that it could prove beneficial were the cytokine storm of Covid-19 ever presents. Health improvement after quitting smoking may be immediate: after 20 min peripheral vasoconstriction is reduced,³⁵ and the heart rate and blood pressure drop. After 12 hours, the carbon monoxide level in the smoker's blood drops to normal and, after 1-9 months, the respiratory ciliary function returns to normal, permitting appropriate clearance of mucus and particulate matter.³⁶ Thus, optimizing baseline physiology through quitting smoking, becomes a natural recommendation for any patient at risk for SARS-CoV-2 infection.

Smoking cessation during the quarantine

Quarantine can provide some barriers to smoking cessation: anxiety associated with the pandemic or, by

means of containment/sheltering in place can trigger an increase in the number of cigarettes smoked. Many groups and support spaces that usually aid smoking cessation intents (i.e., gyms or parks) may be currently closed. In response to this possibility, South Africa and India have banned the sale of tobacco products during lockdown periods. Unfortunately, the illegal market provides cigarette smokers, rendering the measure not fully effective.¹²

Difficult or impossible face-to-face therapeutic interactions due to quarantine adversely affect the possibilities of quitting.³⁷ Nevertheless, isolation may reduce the social induction to smoke³⁸ and, due to the massive closing of stores, product availability can also be reduced,³⁹ while telemedicine may prove to be a useful resource for aiding smoking populations to quit or for the use of mobile applications.⁴⁰

Klemperer and colleagues,⁴¹ who gathered online survey data from 366 tobacco and e-cigarette users, answered some of the previous questions: tobacco consumption was decreased by around 30% of the sample compared to prior to the quarantine, but product availability remained the same for around 50% of smokers, and motivation to quit smoking increased in 35% of the sample while quitting attempts occurred in 22% of all of those surveyed. There was no difference in these outcomes between regular cigarettes and e-cigarette users. Overall, despite stress and isolation, it appears a time appropriate for abandoning smoking.

Despite the health emergency due to Covid-19, the effort to reduce tobacco use should continue,⁴² including all strategies determined by the WHO Framework Convention on Tobacco Control.⁴³ Every smoker should be encouraged to stop smoking and should be provided with advice, support, and pharmacotherapy. Obtaining a complete smoking history is essential for each person tested for Covid-19 and for other respiratory infectious diseases, in order to evaluate the impact of smoking on all aspects of the disease (screening, testing, hospital admission, mechanical ventilation, death, and recovery), with proper adjustment for age, sex, comorbid conditions, and other possible risk factors.⁴²

Conclusions

Limited available research supports the expected increase in the risks of smoking in Covid-19 and the importance of continuing efforts to stop smoking. Improving the outcomes of Covid-19 would likely add to the list of health gains already described in those who have quit smoking. Because it attacks the lungs, the coronavirus that causes Covid-19 represents an especially serious threat to those who smoke tobacco or who vape, given that the

emerging evidence suggests that exposure to aerosols from electronic cigarettes harms the cells of the lung and diminishes the ability to respond to infection. It is crucial for professionals of health to screen history of smoking or vaping in patients who have or are suspected of having Covid-19 for offering cessation alternatives and providing timely follow-up. Overall, health promotion includes stopping tobacco smoking, but also fostering healthy diet, exercise, and avoiding alcohol and addictive substances. Nevertheless, specific evidence between the biological correlations and pathways of smoking with Covid-19 is desperately needed, along with psychosocial evidence of the internal phenomena that smokers undergo during a pandemic, to support effectively a better scheme to reduce smoking prevalence during health crises.

Declaration of conflict of interests. The authors declare that they have no conflict of interests.

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