COVID-19 and TOBACCO: THE UNION'S BRIEF
(Last update: 21 December 2020)

The Union's Tobacco Control Department provides a bi-weekly scientific brief analysing the current science—and any related controversies—regarding COVID-19 and smoking. The briefs will include a short introduction—an overview of the latest science, enumerating trends, key findings and study flaws before delving into specific publications. This master brief, to be updated regularly, is a living document, which synthesises smoking and COVID-19 literature and seeks to summarise a number of important issues. A series of *Frequently Asked Questions* are presented for easy reference.

We identify research studies through searches conducted on PubMed, Google Scholar and websites that publish preprints such as MedRxiv, bioRxiv and Qeios. An expanded search includes article references and comments for the preprints. One challenge in synthesizing the literature is that many of the studies are published as preprints and not yet peer-reviewed. We mark the status of the papers in this review (non-peer-reviewed studies are highlighted) and update them accordingly once they are officially published.

As readers may note, The Union is not the only organization producing a living review on COVID-19 and smoking. The World Health Organization first issued a scientific brief on this subject on 26 May and then an updated brief on 30 June. Simons et al also maintain a living review on smoking and COVID-19 on Qeios.com. WHO chooses to focus only on peer-reviewed papers. The Union's briefs also include non-peer-reviewed papers in preprint, which constitute a large body of the existing literature. We intend to provide an in-depth look at these studies with a focus on their limitations, as some of these studies are frequently cited by the media and may influence policy discussions. Simons et al include non-peer-reviewed studies in their review and also rank the quality of each study, as either fair or poor. A meta-analysis is performed on studies with fair quality. While the approaches used by the three reviews are different, the conclusions are generally aligned.

1. What are the general conclusions we can draw from the current scientific evidence on smoking and COVID-19?

Because there is significant range on the COVID-19 disease spectrum—from infection to death—we attempt to lay out the three stages of disease development and discuss the available evidence and conclusions that can be drawn for each stage of disease development.

Stage 1: Infection with SARS-Cov-2
The relationship between infection and smoking is unclear; clarifying it would require testing large samples of the population to locate asymptomatic cases as well as cases with mild symptoms that do not require hospital visit. To date, only two studies [1] [2] have attempted to address this question and shows early evidence of reduced risk of infection among smokers.

Stage 2: Symptoms emerge, requiring an outpatient visit or hospitalization of 24 hours or more.
The relationship between smoking and progression from stage 1 to this disease stage is unclear though some studies make comparisons between the smoking rates of hospitalized patients and the general population. Such studies are seriously limited; at best, they provide insight into the combined risk of smoking on stages 1-2. Several recently released studies from US [3], UK [4], Denmark [5], and Mexico [6] [7] found that smokers were less at risk for developing symptoms. These studies suffer important limitations. Evidence so far is limited.

Stage 3: Disease progression becomes so advanced it requires ICU admission or mechanical ventilation or results in death.

Most studies so far show a significant association between smoking and progression to this advanced disease stage, but further research is needed.

2. Is smoking associated with lower risk of SARS-Cov-2 infection?

To date, only two studies have attempted to examine the relationship between smoking and SARS-Cov-2 infection. The first is a non-peer-reviewed case-control study from Israel [1] that compares over 4,000 positive COVID-19 cases with matched negative cases (controls) from the patient pool of a major healthcare provider covering more than a quarter of the country's 9 million population. The study found that both current smokers and former smokers were at significantly lower risk than non-smokers for SARS-Cov-2 infection. In addition, the smoking rate (9.8%) among positive patients was lower than the 18% national smoking prevalence. The study also did not find a significant relationship between smoking and severe disease progression.

The study has several strengths: it relies on medical records from the pre-pandemic time; its analysis incorporates many patients who were asymptomatic or had light symptoms; and it compares positive patients to negative patients (the majority of previous studies examine smoking rate among positive patients against the general population). The study does need to clarify the criteria used for COVID-19 testing, i.e. to what extent the people tested represent the infection distribution in the general population. Overall, the design of Israel et al is probably the most robust so far among all studies attempting to address the link between smoking and SARS-Cov-2 infection.

The second study is from Kuwait. Almazeedi et al. [2] used electronic medical records to analyse the clinical characteristics of 1,096 COVID-19 patients from a large hospital. The smoking rate in the sample is 4%, much lower than the general population. Because patients were part of a government-led mass screening effort, the study captured both symptomatic and asymptomatic cases; its ability to include cases from the general population makes it more representative than many studies drawing from a single source. Because tobacco use is not the sole focus of the analysis, smoking is not clearly defined. Question remains as to if former smokers are classified as non-smokers and if water pipe, cigarette, and bidi users are all defined as smokers.

Given the scarcity of evidence at this stage, no conclusion can be drawn about the association between smoking and risk of SARS-Cov-2 infection.

3. Are smokers less likely to get sick from COVID-19?

The best evidence to address this question comes from several recent studies comparing COVID-19 positive cases with negative cases. The Veterans Affairs Hospital in the US did an analysis [3] on 3,789 patients tested for COVID-19 and found that smokers were half as likely to be positive than non-smokers and former smokers combined. It is likely that most if not all the patients tested for COVID-19 already presented with symptoms. A caveat with the interpretation of the finding is that all the sample patients are over 54 years old, with 37% between 70-75.

Similarly, a sentinel network from the UK [4] conducted 3,802 COVID-19 tests and found smokers were half as likely to test positive than non-smokers. The patients tested all had symptoms of influenza or respiratory infections. Another study from the UK [4] with a sample size of 2.4 million found smokers to be more likely to self-report COVID-19 symptoms. Interestingly, among a subset of the sample tested for COVID-19, smokers were less likely to test positive.

The study [5] by Eugen-Olsen et al. evaluated 407 patients in Denmark presenting with COVID-19 symptoms and found a notable difference in smoking rates between those testing positive for the virus (7.1 % current smokers) and those who were negative (27% current smokers). It's important to

be aware that the analysis did not control for age and other covariates. The sample is small and likely not representative of the general population.

The MOH in Mexico made a COVID-19 database available in April. The database consists of patients reported from 475 viral respiratory disease monitoring units from around the country. Six studies [6-11]—none were peer reviewed—used the database for analysis. Two of the six studies [6, 11] performed robust analysis on smoking, both of which determined that smokers were less likely to test positive for COVID-19, and neither found that smokers were more likely to require hospitalization.

There are significant limitations with the database. It did not report information on past smokers, who were likely recorded as "non-smokers." It is unclear how this misclassification may have biased the findings. In addition, because it does not include asymptomatic COVID-19 cases, the database cannot —as Beruman et al. mistakenly use it—be used to estimate infection risk. Instead, the risk estimated is a combination of infection and development of symptoms. Because database inclusion was restricted to patients with respiratory symptoms, patients testing negative for COVID-19 may have higher smoking rates than the general population they come from, thereby biasing the results away from being null. Finally, both COVID-19 positive and negative patients have much lower smoking rates than the general population in Mexico, suggesting systemic under-reporting of smoking on hospital records might be present.

The main advantage with the studies above from US, UK, Denmark, and Mexico is that they all include both positive and negative patients and the studies compare the two groups for risk of smoking. Because we can assume that there was equal potential for bias to misclassify smokers among both positive and negative cases, these studies provide supportive evidence for the hypothesis that smoking is less prevalent among confirmed COVID-19 cases.

Studies that measure smoking rates among positive cases against the general population are weaker, providing less evidence to justify that smokers are at lower risk of COVID-19. Such studies—across China, Asia, the US, and Europe—have found lower smoking rates among hospitalized patients than the general population. For instance, three studies from NYC [12-14] revealed a lower smoking rate of around 5% among COVID-19 patients, compared to 11% in the general population in NYC. The smoking rates among COVID-19 patients in the Chinese studies are generally lower than 15%, as compared to the 30% prevalence among the corresponding age group in the general population [15, 16]. Similar findings have also been reported from UK [17], Switzerland [18] and Italy [6]. On the other hand, several recent studies from Canada [19], UK [20] and [64], Iran [21], and NYC [22] [23] show smoking rates among COVID-19 patients comparable to or higher than the general population. A general limitation of these research studies that only analyze positive cases is that the studied hospital patients may not represent the general population, thus making the smoking rates comparison problematic. The CDC study published in MMWR noted, as one of its limitations, that only 5.8% of the COVID-19 patient records were complete with patient information, including underlying conditions and smoking history [24]. The study from a hospital in France, as another example, is based in a region that also has a lower smoking rate than France's national average [25]. In addition, it is speculated that smokers may conceal their tobacco consumption if they fear that hospitals would not provide resources to patients deemed to have low survival rates.

Several reviews [26-28] attempted to analyse the evidence and propose hypotheses to shed light on this phenomenon. All noted the early stage of research and pointed out the many limitations the studies suffer, most noteworthy of which is the potential of underreporting of smoking history among COVID-19 patients [29]. Many of the available studies are from China, where there is possible underreporting and misreporting of smoking status among COVID-19 patients. According to GATS

China (2018), only 58.3% of smokers who visited a healthcare provider during the past 12 months said they were asked about their smoking history. When hospitals are overwhelmed, as during the COVID-19 outbreak, it is likely that smoking history might not be recorded during admission. A New York City study [30] revealed this problem, as hospital records proved to be an unreliable information source for patient smoking history. Benowitz et al also concluded that US hospital records under-reported the prevalence of smokers among patients [31]. Schofield and Hill found that only 63% of smokers (verified by cotinine test) were correctly recorded in medical records in an Australian study [32]. A London-based hospital study—it missed smoking status data on 29% of patients but found a 6.6% current smoking rate among COVID-19 patients—also highlights the need to question findings derived from hospital records [33]. A case-control study from a UK hospital [65] found that patients hospitalized with COVID-19 had lower odds of being current smokers than patients admitted for respiratory viruses the previous year; the study also found that smoking status was poorly recorded among cases.

Realizing this limitation in previous research, a recent study from Italy made an effort to contact patients or their relatives to confirm smoking history [6]. The authors didn't report the extent of under-reporting of smoking from hospital records, but found similar lower smoking rate among patients than the general population. Finally, a study by Tattan-Birch et al. [63] examines how collider bias—this occurs when researchers control for, stratify on, or select a sample based on a variable that is caused by both the exposure and outcome—impacts COVID-19 research, specifically the finding that smokers (both current and former) appear to be less at risk of testing positive for COVID-19. The underrepresentation of smokers, according to the authors, is likely due to the fact that smokers have a higher likelihood of having a cough (this is the collider), which is indicative of COVID-19 and often included among symptoms that warrant testing. If smokers—compared to non-smokers—are more likely to seek COVID-19 testing even when they do not have the disease, they will be over-represented in the sample with the negative test results, thus making it appear that smokers are less likely to have COVID-19.

A number of studies have attempted to address the relationship between smoking and developing COVID-19. Many have major design limitations; the main concern is the use of hospital records to determine smoking status. A few studies provide more direct but early evidence that smokers might be at less risk to develop COVID-19; these compare patients tested positive with those tested negative, assuming that there is equal potential for bias to misclassify smokers among both positive and negative cases. Further research is needed to clarify this research question.

4. Are hospitalised smokers more likely to suffer worse outcomes from COVID-19?

Important early findings to support this hypothesis appeared 28 February in *The New England Journal of Medicine*. The Guan et al study [34], "Clinical Characteristics of Coronavirus Disease 2019 in China", as later analysed by Vardavas and Nikitara [35], shows that compared to non-smokers, smokers are 2.4 times more likely to be admitted to an intensive care unit, need mechanical ventilation or die.

The first systematic review examining five studies from China by Vardavas and Nikitara [35] concluded "[A]lthough further research is warranted as the weight of the evidence increases, with the limited available data, and although the above results are unadjusted for other factors that may impact disease progression, *smoking is most likely associated with the negative progression and adverse outcomes of COVID-19."*

Patanavanich and Glantz conducted a meta-analysis of 12 published papers to determine the association between smoking and COVID-19 progression [15]. The authors focused on studies on smoking behaviour and COVID-19 disease progression published between 1 January and 6 April. In

total, the meta-analysis reports on 9,025 COVID-19 patients, including 495 patients with a history of smoking. Of the patients with this history, a total of 88 (17.8%) experienced disease progression, compared with 9.3% of never smoking patients. The authors wrote: *"[S]mokers hav[e] 2.25 times the odds of severe COVID-19 outcomes than never smokers."*

Five more meta-analyses [36-40] that have been published since came to similar conclusions as previous meta-analyses. All found smoking history to be associated with elevated risk of severe outcomes of COVID-19.

The current evidence strongly suggests hospitalised smokers with COVID-19 may have worse outcomes than non-smokers.

5. How does e-cigarette use impact COVID-19?

Only one study has attempted to investigate the relationship between e-cigarette use and risk of COVID-19. Gaiha et al [41] received significant media attention for their study examining the relationship between use of e-cigarettes, cigarettes, and dual usage with COVID-19 symptoms, testing, and diagnosis among 4,351 young people aged 13-24. Using an online cross-sectional multivariate logistic regression, the researchers found that a COVID-19 diagnosis was nearly 7 times more likely among dual-users who had smoked cigarettes and vaped within the past 30 days. Testing was 9 times more likely among past 30-day dual users and 2.6 times more likely among past 30-day users of e-cigarettes. Symptoms were nearly 5 times more likely among past 30-day dual users. Because cigarette smoking by itself was not associated with the three outcomes and past 30-day use of e-cigarettes was not associated with COVID-19 diagnosis or symptoms, the authors concluded that dual use presents the greatest risk. Though the authors control for confounders such as BMI and SES, the study suffers several limitations, including self-reporting, wide confidence intervals, and some imprecise conclusions on the relationship between dual use and testing and diagnosis. Further research is needed to clarify the risk of e-cigarette use on COVID-19.

6. Are there any clinical and laboratory data showing the impact of smoking on SARS-Cov-2 infection and COVID-19?

Clinical and laboratory data is also missing as part of the evidence base to support or reject the hypothesis that smoking or nicotine protects against SARS-Cov-2 infection. It is generally accepted that SARS-Cov-2, the virus that causes COVID-19, enters human cells through ACE2, the same receptor for SARS-Cov [42]. Researchers are less in agreement about whether smoking and nicotine upregulates or downregulates the activity of ACE2 [43-51] [52] [53] [67] [68] which, presumably affects the chance that SARS-Cov-2 enters cells. In examining ACE2 expression among current smokers and current e-cigarette users, Lee et al. [54] found that while ACE2 expression was upregulated among the former, this was not the case with the latter. Similarly, Zhang et al [55] showed that non-smokers exposed to e-cigarette vapor (with and without nicotine) showed no ACE2 expression change. This finding warrants further research as the authors contest that constituents in tobacco other than nicotine might be responsible for ACE2 upregulation among smokers. And, while supporting the theory that ACE2 is the main entry point for SARS-CoV-2, Zamorano et al.'s work [66] recognize that the receptor is, at most, poorly expressed in cell respiratory epithelium. Co-receptors—NRP1, HS, or sialic acids—exposed at target cell surfaces may help explain a two-step attachment mechanism.

Hikmet et al [56] mapped ACE2 levels in various body tissues and observed zero or minimal levels in the respiratory system but much higher levels in other tissues—intestine, colon, and kidney. The

researchers maintain that SARS-cov-2 infection may occur through alternate receptors or even non-receptor dependent mechanisms. Both Changeux [57] and Tizabi et al [58] argue that another receptor—nAchR—may play a key role in SARS-Cov-2 infection and that nicotine may compete with or even block the binding of SARS-Cov-2 to nAchR, thus lowering smokers' chance of infection.

It should be noted that there is little consensus regarding whether any tobacco smoke constituents, particularly nicotine, interplay with the SARS-Cov-2 infection mechanism. The hypotheses by Changeux and others are backed by either conflicting or very limited evidence.

In an in vitro study, Purkayastha et al. [59] observed increased SARS-Cov-2 infection in airway cells when exposed to tobacco smoke. They also determined that when airway epithelial cells are infected with SARS-COV-2, interferon response genes are induced but when cells are infected with the virus and exposed to cigarette smoke, the interferon response is reduced, producing more severe viral infection and cell death.

The current evidence is far from conclusive, and it would be erroneous to infer any relationship between SARS-Covid-2 infection, COVID-19 and nicotine (or any other tobacco smoke constituents).

7. What are the French studies?

In late April, three studies—1) the "Pasteur Institute paper," a retrospective study from a Oise high school [60]; 2) a study from a Paris hospital, Low Incidence of Daily Active Tobacco Smoking in Patients with Symptomatic COVID-19 [25]; and 3) Jean-Pierre Changeux's "A nicotinic hypothesis for COVID-19" [57]—were released, garnering significant media attention for bold claims that *nicotine use and/or smoking may have a protective effect against COVID-19 infection.* The two French researchers who authored the third paper with the "Nicotinic Hypothesis" also announced that they would begin a human trial on 1500 health professionals [61].

The studies (see chart below) occupied headlines, confused people, put tobacco control advocates on the defensive, and even resulted in people panic buying nicotine. In response, France decided to limit nicotine sales between 26 April and 11 May for fear that nicotine gum and patches would be either misused or unavailable to those who needed them for smoking cessation [62].

These studies are fraught with a number of serious problems:[1]

Study	Publication	Synopsis	Study and Design Flaws

[1] The analysis below builds on and synthesises findings provided by colleagues at WHO and STOP. For the WHO statement on tobacco use and COVID-19, please see: https://www.who.int/news-room/detail/11-05-2020-who-statement-tobacco-use-and-covid-19#.XrlJGqgsEvs.email. For the STOP press release, please see https://exposetobacco.org/news/flawed-covid19-studies/

"Cluster of COVID-19 in northern France: A retrospective closed cohort study"	23 April, 2020 Medrxiv preprint	This retrospective, closed cohort study of a heavily impacted community in Oise, France involved a questionnaire that covered history of fever and respiratory systems and also examined blood, with collection from two centers, for anti-SARS-CoV-2 antibodies. The study involved 661 participants with a median age of 37 and the infection attack rate (IAR) was defined as "the proportion of participants with confirmed SARS-Co-V-2 infection based on antibody detection." The study concluded that smokers were less likely (7.2%) to be infected with the virus than non-smokers (28%).	This study involved a small sample size, likely involved selection bias, and a large number of participants who, because they were under the legal age for tobacco use, were likely inclined to not self-report its consumption. Tests used to report antibodies were not validated, increasing the likelihood that they produced results. And, key variables—attendance at the school where there was a COVID-19 outbreak—were conveniently ignored.
"Low Incidence of Daily Active Tobacco Smoking in patients with Symptomatic COVID-19"	21 April, 2020 Qeios.com No peer review	Miyara et al. state that their objective was to "evaluate the correlation of daily smoking with the susceptibility to develop SARS-CoV-2 infection." Their study examined both inpatients (343) and outpatients (139) with confirmed COVID-19 at a large French University Hospital in Paris. Because the proportion of daily smokers among the study group was significantly lower (5.3%) compared to the general population of France (25.4%), the authors conclude that *"daily smokers have a very much lower probability of developing symptomatic or severe SARS-CoV-2 infection as compared the general public."*	The study has several significant limitations. The first involves sample bias and the fact that the studied group excluded patients in the intensive care unit, who would comprise the most seriously ill and who might present as smokers at much higher rates. Second, studies set in hospitals are far from ideal—they include very localised populations, including healthcare workers, who comprised a significant number of studied cases. This cohort is most likely to become infected in the hospital, which reveals minimal information about community infection. Finally, the study focuses on present smokers, emphasising that 22/482 COVID-19 patients were daily smokers—a lower proportion than expected—but makes an egregious mistake by ignoring that nearly 60% of patients (285) were former smokers and 12 were occasional smokers.

"A Nicotinic Hypothesis for COVID-19 with preventive and therapeutic implications"	21 April, 2020 Qeios.com No peer review	Authored by Changeux et al. this offers a new hypothesis based on the same findings from the Paris hospital study of 482 COVID-19 patients. In their introductory paragraph, the authors "hypothesise that the nicotinic acetylcholine receptor (nAChR) plays a key role in the pathophysiology of Covid-19 infection and might represent a target for the prevention and control of Covid-19 infection." In their concluding paragraph, the authors acknowledge that smoking "remains a serious danger for health" yet they also make the case that desperate times call for desperate measures; their final sentiment is that "under controlled settings, nicotinic agents could provide an efficient treatment for an acute infection such as Covid-19."	This paper does not actually test its hypothesis, nor does it offer any evidence to support it. In addition, as others, including STOP, have noted, the author Jean-Pierre Changeux has long-standing historical links to the tobacco industry.

Please contact Megan Quitkin (megan.quitkin@theunion.org) if you have any questions about this brief.

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