COVID-19 AND SMOKING: THE UNION BRIEF
Issue #3 (29 June 2020)

This third brief synthesizes the most recent studies, analysing research published between the last Union brief (1 June) and today. In total, the team reviewed over 100 articles with findings on the relationship between smoking and COVID-19. Here is a summary of the findings:

- **Infection with SARS-Cov-2:** A recent non-peer-reviewed case-control study suggests that smokers might be at lower risk of infection. To our knowledge, this is the first study to include asymptomatic cases and cases with light symptoms in the analysis. Please see below for details.
- **COVID-19 Progression, including hospitalization:** Several newly released studies from Denmark, Mexico, and Poland suggest that the risk of developing COVID-19 symptoms might be lower among smokers. These studies—and their limitations-- are discussed in detail below.
- **Severe Disease Outcomes:** Most recent studies suggest that smoking facilitates severe disease progression and death.
- **Biochemistry:** Evidence continues to show a positive relationship between nicotine and ACE2 expression. A new, non-peer-reviewed study shows a dose-response relationship—as a smoker's pack years increases, so does their ACE2 expression.
- **Conclusion:** As indicated in the chart below, there are major gaps in understanding the links between smoking and COVID-19; we identify three key disease stages, noting where smoking data is available, as well as critically needed. The Union maintains its previous positions with regard to smoking and COVID-19.

The COVID-19 Disease Spectrum: Three Stages of Development

Disease Stage and Definition	Research to date (and what's needed)
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 a hospital visit. To date, only one study with a case-control design has attempted to address this question; it 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. Several recently released studies from Denmark and Mexico found less risk for smokers to develop symptoms. These studies suffer important limitations. Evidence so far is limited.
Stage 3: Advanced disease progression requiring ICU admission or mechanical ventilation or results in death	Most studies show a significant association between smoking and progression to this advanced disease stage.

Smoking and SARS-Cov-2 Infection

A recent non-peer-reviewed case-control study from Israel[1] compared over 4,000 COVID-19 positive 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 significantly lower smoking rates (9.8%) among positive patients, as compared to the 18% national smoking prevalence; it did not find a significant relationship between smoking and severe disease progression. Most importantly, the study found that both current smokers and former smokers were at significantly lower risk than non-smokers for SARS-Cov-2 infection.

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.

Smoking and Development of COVID-19

Denmark Study

The study[2] by Eugen-Olsen et al. evaluated 407 patients 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). Because we can assume that there was equal potential for bias to misclassify smokers among both positive and negative cases, this study further bolsters the hypothesis that smoking is less prevalent among confirmed COVID-19 cases. 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.

Mexico studies

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[345678]—none were peer reviewed—used the database for analysis. Two of the six studies[9 10] performed robust analysis on smoking; both determined that smokers were less likely to test positive for COVID-19, and neither found that smokers were more likely to require hospitalization.

The main advantage of the Mexican database is that it includes both positive and negative patients, and the studies compare the two groups for risk of smoking, whereas most previously published studies rely on the comparison between hospitalized patients and the general population. However, 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 in hospital records might be present.

Poland study

This study[11] reported an 11.2% current smoking rate among non-hospitalized COVID-19 patients, as compared to the 21% in the general population. The study did not include negative cases thus comparison with positive cases was not possible. The study's strength is a cross-sectional design that includes all non-hospitalized COVID-19 patients in Poland up to April 17, 2020.

In contrast to aforementioned research that compares COVID-19 positive and negative cases, studies that measure smoking rates among positive cases against the general population provide weaker evidence to justify the decreased risk among smokers. Twenty-one studies on smoking and COVID-19 hospitalization were recently published, including 11 peer-reviewed. The studies from Canada (peer-reviewed)[12] and Iran (non-peer-reviewed)[13] show smoking rates among COVID-19 patients *comparable* to the general population. A study from New York City (peer-reviewed)[14] also produced this finding. Several studies (all non-peer-reviewed) from countries not previously discussed in The Union briefs—Spain,[15 16] Belgium,[17] Kuwait,[18] and Israel[19 20]—show hospitalized COVID-19 patients presenting with *lower* smoking prevalence than found in the general population. Two additional studies from China (both peer-reviewed)[21 22] also show a lower smoking prevalence among patients.

These 21 studies suffer from some of the same issues present in studies included in briefs 1 and 2: many are not peer reviewed and only include data for hospitalized patients. Two newly identified studies show further evidence that hospital records may not be a reliable source of information for smoking status. Schofield and Hill found that

only 63% of smokers (verified by cotinine test) were correctly recorded in medical records. 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.

Smoking and Severe Disease Progression from COVID-19

We reviewed eleven new studies[23] [24] [25] [26] [27] [28] [29](three of which were peer-reviewed) on COVID-19 disease progression; these are aligned with studies in briefs 1 and 2 demonstrating that smokers have worse disease outcomes, including death. A Kuwait study (non-peer-reviewed) found that while smokers comprised just 4% of a 1,096 sample, they were more likely to die or be admitted to an ICU. A study from New York City (non-peer-reviewed) produced similar findings: there was a 3.5% smoking rate among 5000 hospital patients but "death from COVID-19 was associated with smoking." And, a peer-reviewed article from Spain found that in a population of over 2,000 hospitalized patients, there was a significant difference in the smoking rate between patients who died (9.6% current smokers) and those who were discharged (6.4% current smokers).

In addition, two studies from Mexico and two from Israel found no evidence of increased risk among smoking for disease progression (see above for detailed analysis of the studies under "Smoking and SARS-Cov-2 Infection" and "Smoking and Development of COVID-19 Symptoms").

UK Study

A non-peer reviewed study by Williamson et al. examined 17 million patient records to determine risk factors for 5,683 COVID-19 fatalities. There was a significant positive relationship between death and smoking or former smoking but only when the statistical model adjusted for age and sex. When further adjustment was made for other covariates, including COPD, which was the major contributor to adjusted hazard ratio, smoking no longer proved significant in causing death. Because COPD and smoking are inextricably linked, it's debatable whether the disease should be adjusted for, but to their credit, the authors did not draw major conclusions about smoking and omitted this discussion among their main findings. Interestingly, FSFW President Derek Yach cited Williamson et al during a WNTD radio interview; in addition to going off message for the Foundation, which purports to recognise the dangers of smoking, Yach misrepresented the study, suggesting it bolsters claims that smokers are at *lower* risk of COVID-19 death than former smokers.

Biochemical Studies

Four new, non-peer-reviewed studies [30] [31] [32] reinforce previous findings on the relationship between nicotine, increased ACE2 expression and the potential for SARS-Cov-2 to invade smoker's cells. Smith et al further explored this dynamic, showing that there may be a dose-response relationship at play so that as a smoker's pack-years increases, so too does their ACE2 expression and virus vulnerability.

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[1] Israel A, Feldhamer I, Lahad A, et al. "Smoking and the risk of COVID-19 in a large observational population study." *MedRxiv*. 2020. doi:https://doi.org/10.1101/2020.06.01.20118877

[2] "Low levels of the prognostic biomarker suPAr are predictive of midl outcome in patients with symptoms of COVID-19—a prospective cohort study" https://www.medrxiv.org/content/10.1101/2020.05.27.20114678v1.full.pdf

[3] Theodoros Giannouchos, Roberto Sussman, Jose Manuel Mier, Konstantinos Poulas, Konstantinos Farsalinos. "Characteristics and risk factors for COVID-19 diagnosis and adverse outcomes in Mexico: an analysis of 89,756 laboratory-confirmed COVID-19 cases." medRxiv 2020.06.04.20122481; doi: https://doi.org/10.1101/2020.06.04.20122481

[4] "Early estimation of the risk factors for hospitalisation and mortality by COVID-19 in México." https://www.medrxiv.org/content/10.1101/2020.05.11.20098145v1.full.pdf

[5] "Predicting mortality due to SARS-CoV-2: A mechanistic score relating obesity and diabetes to COVID-19 outcomes in Mexico." https://www.medrxiv.org/content/10.1101/2020.04.20.20072223v4.full.pdf

[6] "COVID-19 Fatality and Comorbidity Risk Factors among Diagnosed Patients in Mexico." https://www.medrxiv.org/content/10.1101/2020.04.21.20074591v1

[7] Berumen J, Schmulson M, Alegre J, et al. "Risk of infection and hospitalization by COVID-19 in Mexico: A case-control study." *MedRxiv*. 2020. Doi: https://doi.org/10.1101/2020.05.24.20104414

[8] "Non-communicable diseases and inequalities increase risk of death among COVID-19 patients in Mexico." https://www.medrxiv.org/content/10.1101/2020.05.27.20115204v1.full.pdf
[9] Berumen J, Schmulson M, Alegre J, et al. "Risk of infection and hospitalization by COVID-19 in Mexico: A case-control study." *MedRxiv*. 2020. Doi: https://doi.org/10.1101/2020.05.24.20104414
[10] Gutierez and Bertozzi. "Non-communicable diseases and inequalities increase risk of death among COVID-19 patients in Mexico." https://www.medrxiv.org/content/10.1101/2020.05.27.20115204v1.full.pdf
[11] "Gender differences in the frequency of gastrointestinal symptoms and olfactory or taste disorders among 1,942 non-hospitalized patients with COVID-19." *Polish Archives of Internal Medicine.* 2020. Doi: https://dx.doi.org/10.20452/pamw.15414 https://www.mp.pl/paim/issue/article/15414
[12] "Anosmia and dysgeusia associated with SARS-CoV-2 infection: an age-matched case–control study." https://www.cmaj.ca/content/early/2020/05/27/cmaj.200869
[13] "A One-year hospital based prospective COVID-19 open cohort in the Eastern Mediterranean region: The Khorshid COVID Cohort (KCC) study." https://www.medrxiv.org/content/10.1101/2020.05.11.20096727v2.full.pdf
[14] "Observational study of hydroxychloroquine in hospitalized patients with Covid-19." *New England Journal of Medicine.* https://www.nejm.org/doi/full/10.1056/NEJMoa2012410?query=featured_coronavirus
[15] "Clinical characteristics of patients hospitalized with COVID-19 in Spain: results from the SEMICOVID-19 Network." https://www.medrxiv.org/content/10.1101/2020.05.24.20111971v1.full.pdf
[16] "A Cohort of Patients with COVID-19 in a Major Teaching Hospital in Europe." *Journal of Clinical Medicine.* 2020; 9 (6): 1733. Doi: https://doi.org/10.3390/jcm9061733
[17] "The relation between ACEI/ARB use and COVID-19 severity RT-PCR-confirmed cases: A retrospective case-control study." https://www.researchsquare.com/article/rs-33177/v1
[18] "Clinical Characteristics, Risk Factors and Outcomes Among the First Consecutive 1,096 Patients Diagnosed with COVID-19: The Kuwait Experience." https://www.medrxiv.org/content/10.1101/2020.05.09.20096495v1.full.pdf
[19] Israel A, Feldhamer I, Lahad A, et al. "Smoking and the risk of COVID-19 in a large observational population study." *MedRxiv*. 2020. doi:https://doi.org/10.1101/2020.06.01.20118877
[20] Yanover C, Mizrahi B, Kalkstein N, et al. "What factors increase the risk of complications in SARS-CoV-2 positive patients? A cohort study in a nationwide Israeli health organization." MedRxiv. 2020. doi: https://doi.org/10.1101/2020.05.07.20091652
[21] Mao B, Liu Y, et al. "Assessing risk factors for SARS-CoV-2 infection in patients presenting with symptoms in Shanghai, China: a multicenter, observational cohort study." *The Lancet*. 2020. Doi: https://doi.org/10.1016/ https://www.thelancet.com/pdfs/journals/landig/PIIS2589-7500(20)30109-6.pdf
[22] "Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre retrospective cohort study." https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(20)30309-0/fulltext
[23] https://www.researchsquare.com/article/rs-31123/v1
[24] "Morbid Obesity as an Independent Risk Factor for COVID-19 Mortality in Hospitalized Patients Younger than 50." *Obesity*. 2020. Doi: https://doi.org/10.1002/oby.22913
[25] Hu L, Chen S, et al. "Risk Factors Associated with Clinical Outcomes in 323 COVID-19 Hospitalized Patients in Wuhan, China." *Clinical Infectious Diseases*. 2020. Doi: https://doi.org/10.1093/cid/ciaa539 https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa539/5828282?searchresult=1
[26] Borobia A, Carcas A, et al. "A Cohort of Patients with COVID-19 in a Major Teaching Hospital in Europe." *Journal of Clinical Medicine.* 2020; 9 (6): 1733. Doi: https://doi.org/10.3390/jcm9061733
[27] Mehra M, Desai S, et al. "Cardiovascular Disease, Drug Therapy and Mortality in COVID-19." *The New England Journal of Medicine*. 2020. Doi: https://www.nejm.org/doi/full/10.1056/NEJMoa2007621
[28] "Clinical predictors of COVID-19 mortality." https://www.medrxiv.org/content/10.1101/2020.05.19.20103036v1.full.pdf
[29] Clinical Characteristics, Risk Factors and Outcomes Among the First Consecutive 1,096 Patients Diagnosed with COVID-19: The Kuwait Experience. https://www.medrxiv.org/content/10.1101/2020.05.09.20096495v1.full.pdf
[30] Pino L, Triana I, Perez C, et al. "Electronic nicotine delivery systems (ECs) and COVID-19: the perfect storm for young consumers." *Clinical and Translational Oncology*. 2020. doi: https://dx.doi.org/10.1007%2Fs12094-020-02391-x
[31] Chakladar J, Shende N, Li W, et al. "Smoking-Mediated Upregulation of the Androgen Pathway Leads to Increased SARS-CoV-2 Susceptibility." *International Journal of Molecular Sciences.* 2020 21(10):3627. doi: https://doi.org/10.3390/ijms21103627
[32] Breidenbach J, Dube P, Ghosh S, et al. "Impact of Comorbidities on SARS-CoV-2 Viral Entry-Related Genes." *BioRxiv*. 2020. doi:https://doi.org/10.1101/2020.05.26.117440