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Brief Report

Current Smoking and Risk of Coronavirus Infection and Illness in a Highly Controlled Challenge Study: A Re-analysis of the British Cold Study

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Abstract

Introduction: Meta-analyses have shown an association between smoking and the risk of Coronavirus Disease 2019 (COVID-19) disease severity, but the risk of smoking and coronavirus infection is less clear.

Aims and Methods: We re-analyzed data from the British Cold Study, a 1986–1989 challenge study that exposed 399 healthy adults to 1 of 5 "common cold" viruses (including $n = 55$ for coronavirus 229E). Participants with cotinine levels below 15 ng/mL (noncurrent smokers) were compared with participants with higher cotinine levels or self-reported smoking (current smokers). We calculated overall and coronavirus-specific unadjusted and adjusted relative risks (RRs) for current smoking and each outcome (infection and illness), and tested whether each association was modified by the type of respiratory virus.

Results: Current smokers had a higher adjusted risk than noncurrent smokers for infection (adjusted RR [aRR] = 1.12, 95% CI: 1.01, 1.25) and illness (aRR = 1.48, 95% CI: 1.11, 1.96). Neither association was modified by an interaction term for smoking and type of virus (infection: $p = .44$, illness: $p = .70$). The adjusted RR estimates specific to coronavirus 229E for infection (aRR = 1.22, 95% CI: .91, 1.63) and illness (RR = 1.14, 95% CI: .62, 2.08) were not statistically significant.

Conclusions: These RRs provide estimates of the strength of associations between current smoking and infection and illness that can be used to guide tobacco control decisions.

Implications: Systematic reviews and meta-analyses have found an association between smoking and COVID-19 disease severity, but fewer studies have examined infection and illness. The British Cold Study, a high-quality challenge study that exposed healthy volunteers to respiratory viruses including a coronavirus, provides an opportunity to estimate the RR for current smoking and infection and illness from coronaviruses and other viruses to guide tobacco control decisions. Compared with noncurrent smokers, current smokers had a 12% increased risk of having a laboratory-confirmed infection and a 48% increased risk of a diagnosed illness, which was not modified by the type of respiratory virus including a coronavirus.

Introduction

Systematic reviews and meta-analyses have found an association between current and former smoking and increased severity of Coronavirus Disease 2019 (COVID-19) illness, compared with never smokers.[1–5] However, the risk of smoking and infection and reinfection are less clear. One meta-analysis reported a reduced risk of infection among current smokers.[5] Therefore, there is a need for data from high-quality studies to quantify the association between smoking and the risk of infection with the novel coronavirus that causes COVID-19.[6]

The British Cold Study (BCS) has been the only high-quality study completed to date, in which healthy volunteers were experimentally exposed to respiratory viruses (including a coronavirus).[7,8] The US Surgeon General describes studies of particular interest as those "… in which human volunteers were infected with clinically relevant viral pathogens under controlled experimental conditions," and this study contributed to the conclusion that smoking is causally associated with an increased risk of respiratory infections.[9] The BCS challenged individuals with coronavirus 229 E, an endemic upper respiratory infection that causes mild illness and has a different receptor and so, potentially, tissue route of entry than SARS-CoV-2.[10]

While the BCS found an increased odds of respiratory infection and illness among current smokers compared with nonsmokers, odd ratios may overestimate the strength of the association if the event is not rare (> 10%)[11,12] and no results were reported by type of virus. The relative risk (RR) can provide an estimate of the strength of associations that can guide tobacco control decisions. Therefore, we re-analyzed data from the BCS to estimate the RRs between smoking, infection, and illness, and whether these associations differed for a coronavirus compared with other viruses.

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Aims and Methods

Data Source

The BCS was conducted from 1986 to 1989 and is now a publicly available dataset. Its methods have been previously described.[7,8] In brief, 399 participants were quarantined for 2 days before and 7 days after nasal inoculation with one of five respiratory viruses: rhinovirus (types 2, 9, and 14), respiratory syncytial virus (RSV), or coronavirus 229E (CoV229E). Three participants were missing smoking status, resulting in a final sample size of 396.

Smoking Status

Current smoking status was biochemically measured using serum cotinine, a metabolite of nicotine, measured 2 days before and 28 days after inoculation. Participants were classified as current smokers if the average of their two cotinine measurements was 15 ng/mL or higher[13] or if they self-reported being a current smoker. For this study, nine self-reported nonsmokers with cotinine ≥ 15 ng/mL and five self-reported current smokers with cotinine < 15 ng/mL were classified as current smokers.

Outcomes

Two outcomes were examined: Laboratory-confirmed infection and clinically diagnosed illness. Adults were classified as infected if they had (1) a four-fold increase in antibody titers to the challenge virus and/or (2) viral shedding was detected using a culture, a less sensitive methodology than currently used PCR methods.[14] Adults were classified as having the illness, in addition to infection, if they had a physician diagnosis of a cold within up to 28 days after inoculation.

Covariates

Covariates included seropositivity for the viruses before the challenge, age (18–24, 25–29, 30–34, 35–39, 40–44, and 45–54 years), sex, education (none or primary, secondary, some university, university graduate or more), self-reported allergy to food or drug, body mass index (BMI) (< 25, 25–29, or >= 30 years), season (daylight hours on the first day of the trial), number of roommates, number of infected roommates, virus type, and average number of alcoholic drinks per day (0, 0.1–1, 1.1–2, or > 2). Information on race/ethnicity was not collected.

Statistical Analysis

The relative risk for smoking and each outcome was calculated using SAS PROC GENMOD's log-binomial regression[11] with SAS Version 9.4. Model 1 was unadjusted, model 2 adjusted for age and sex, and model 3 additionally adjusted for allergy to food or drug, season, number of roommates, and virus type. Model 4 additionally adjusted for the following potential intermediate variables: seropositivity for the virus, number of infected roommates, BMI, education, and alcohol. To examine if each association was modified by the type of virus, an interaction term (smoking*type of virus) was included in model 4 for each outcome.

Results

The study participants were about two-thirds female (61.7%) and not married (66.1%). The mean age was 33.6 years. Almost a quarter (25.7%) had at least some university education. The majority were not overweight with a BMI < 25 (73.5%). Most participants had a roommate (one: 59.6%, two: 33.3%). Over a quarter of participants were current smokers (28.3%) and almost two-thirds reported drinking alcohol (62.8%).

Table 1 shows that most participants (82.3%) developed a laboratory-confirmed infection, with a higher proportion of infection among current smokers (smokers: 88.4%, nonsmokers: 79.9%). In the fully adjusted (Model 4), the risk for infection was 12% (95% CI: 1%, 25%) higher in current smokers compared with noncurrent smokers. The adjusted risk for infection specific to coronavirus 229E was not statistically significant (RR: 1.22, 95% CI: .91, 1.63). The association between smoking and infection was not modified by the type of virus (interaction term $p = .44$).

Table 1 shows that over a third of participants (38.1%) were diagnosed with an illness, with a higher proportion of illness among current smokers (smokers: 42.0%, nonsmokers: 36.6%). The adjusted risk (Model 4) for illness was 48% (95% CI: 11%, 96%) higher in current smokers compared with non-current smokers. The adjusted risk of illness-specific to coronavirus 229E was not statistically significant (RR: 1.14, 95% CI: .62, 2.08). The association between current smoking and illness was not modified by the type of virus (interaction term $p = .70$).

Discussion

This is the first high-quality study to show that current smokers, compared to non-current smokers, have an increased risk of laboratory-confirmed viral infection (RR = 1.12, 95% C.I 1.01–1.25) and clinically diagnosed illness (RR = 1.48, 95% C.I. 1.11–1.96). For the 55 participants challenged with coronavirus 229E, there was no statistically significant increase in risk for current smokers compared with non-current smokers. Our results for the association between smoking and illness are consistent with the original BCS findings, which calculated an adjusted odds ratio of 2.08 (95% CI: 1.18, 3.70).[8] Our study's RRs are lower than the original study's odds ratio, as the odds ratio overestimates the risk ratio when the outcome is not rare (> 10%), as was the case for both infection and illness.[11,12] The fully adjusted relative risks and 95% confidence intervals reported here for infection (1.12, 95% CI: 1.01, 1.25) and illness (1.48, 95% CI: 1.11, 1.96) can provide an estimate of the magnitude of association, which may help guide tobacco control and SARS-CoV-2 challenge study decisions until other high-quality data is available. For example, the first SARS-CoV-2 human challenge trial intentionally exposed 36 healthy volunteers aged 18 to 29 years in the United Kingdom.[15,16]

Our findings are consistent with an observational study that reported a RR of 1.88 (95%: 1.49–2.38) for the association between smoking and COVID-19 infection among younger adults (aged 49–68 years), but no association for adults 69–86 years.[17] Contrary to our results, a cross sectional study on a navy aircraft carrier reported a decreased odds of COVID-19 infection comparing current smokers to never smokers (OR 0.64, 95% CI: .49, .84).[18] However, the authors note this odds ratio was an overestimate of the RR, as the outcome was high with 76% infected. In addition, a "living rapid review" and meta-analysis reported a similar decreased risk between current smoking and COVID-19 infection (RR = 0.71, 95% CI: .61, .82).[5] However, only 3 of the 30 included

Table 1. Association Between Smoking and Respiratory Virus Infection and Illness, British Cold Study

	n	Percent	Model type			
			Model 1 (*n* = 396)	Model 2 (*n* = 396)	Model 3 (*n* = 396)	Model 4 (*n* = 373)
Infection						
Total	396	82.3				
Smoker						
Yes	112	88.4	1.11 (1.01, 1.21)	1.10 (1.00, 1.21)	1.09 (0.99, 1.19)	1.12 (1.01, 1.25)
No	284	79.9	ref	ref	ref	ref
Coronavirus 229E	55	90.9				
Smoker						
Yes	20	95.0	1.07 (0.92, 1.25)	1.06 (0.89, 1.27)	1.19 (0.94, 1.51)	1.22 (0.91, 1.63)
No	35	88.6	ref	ref	ref	ref
Other viruses	341	80.9				
Smoker						
Yes	92	87.0	1.10 (1.0, 1.22)	1.10 (0.99, 1.22)	1.09 (0.98, 1.22)	1.14 (1.01, 1.28)
No	249	78.7	ref	ref	ref	ref
Illness						
Total	396	38.1				
Smoker						
Yes	112	42.0	1.15 (0.88, 1.50)	1.19 (0.91, 1.57)	1.13 (0.86, 1.47)	1.48 (1.11, 1.96)
No	284	36.6	ref	ref		
Coronavirus 229E	55	61.8				
Smoker						
Yes	20	60.0	0.95 (0.62, 1.48)	0.95 (0.63, 1.44)	1.11 (0.68, 1.80)	1.14 (0.62, 2.08)
No	35	62.9	ref	ref	ref	
Other viruses	341	34.3				
Smoker						
Yes	92	38.0	1.16 (0.84, 1.58)	1.18 (0.85, 1.64)	1.14 (0.83, 1.58)	1.49 (1.06, 2.10)
No	249	32.9	ref	ref	ref	

Model 1 = unadjusted.
Model 2 = adjusted for age and sex.
Model 3 = additionally adjusted for allergy to food or drug, season, number of roommates, virus type.
Model 4 = additionally adjusted for seropositivity for the viruses before the challenge, number of infected roommates, education, BMI, and alcohol consumption.
Participants were classified as smokers if the average of two serum cotinine measurements was 15 ng/mL or higher or if they self-reported being a current smoker.
Other viruses included RSV, RV 14, RV 9, and RV 2.

studies were categorized as being "good" quality, which would reflect having <20% missing data on smoking status, distinct smoking status categories, using biochemical verification of smoking status and reported adjusted results, or using a representative or random sample.[5] In addition, the authors reported several limitations, including that current smokers may be more likely to get tested due to increased symptoms, smoking status in electronic health records may be underreported, or individuals with COVID-19 may have stopped smoking immediately prior to testing or hospitalization and recorded as a non or former smoker (reverse causation).

Limitations of our study include the fact that the participant selection criteria and the highly controlled environment may limit the generalizability. The number of participants challenged with coronavirus 229E was small ($n = 55$), which may have contributed to the wide confidence intervals for the RR between smoking and coronavirus 229E infection and illness. Most importantly, the coronavirus 229E may have different biological and health effects than other coronaviruses including SARS-CoV-2. Thus, the findings may not be generalizable to other coronaviruses.

Conclusion

In a high-quality challenge study, current smokers had an increased risk of respiratory viral infection and illness, with no significant difference across several virus types including a coronavirus. These findings are consistent with known harms caused by smoking to immune and respiratory defenses and some observational evidence of increased COVID-19 infection and disease progression in current smokers. Addressing tobacco use may have implications for COVID-19 at the population level, as a quarter (25.2%) of the US population are current smokers.[19] In combination, the past and current findings support urgent recommendations to increase tobacco control efforts for countering the COVID-19 pandemic.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at https://academic.oup.com/ntr.

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Declaration of Interests

None declared.

Author Contributors

M.D., E.T., and B.L. conceptualized the study. N.K. conducted a literature review. M.D. analyzed the data and wrote drafts. All authors made edits and approved the final draft before submission.

Data Availability

The British Cold Study data are publicly available at the following website: https://www.cmu.edu/common-cold-project/

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