Research Report

Associations between Tobacco Smoking and Self-Reported SARS-CoV-2/COVID-19 Infections, Disease Severity, and Duration in the German Population

Daniel Kotz[1,2], Olga Perski[2], Kathleen Gali[3,4], Jamie Brown[2], and Sabrina Kastaun[1,5]

[1] Addiction Research and Clinical Epidemiology Unit, Institute of General Practice (ifam), Centre for Health and Society (chs), Medical Faculty and University Hospital Düsseldorf, Heinrich Heine University Düsseldorf, Germany
[2] Department of Behavioural Science and Health, University College London, United Kingdom
[3] Hamburg Center for Health Economics, University of Hamburg, Germany
[4] University Cancer Center Hamburg, University Medical Clinic Hamburg-Eppendorf, Germany
[5] Patient-Physician Communication Research Unit, Institute of General Practice (ifam), Centre for Health and Society (chs), Medical Faculty and University Hospital Düsseldorf, Heinrich Heine University Düsseldorf, Germany

Abstract: *Background:* Our aim was to assess, in the general German population, the association between tobacco smoking status and self-reported SARS-CoV-2 infection, COVID-19 symptom severity, and symptom duration. *Methods:* Cross-sectional household survey with face-to-face interviews of representative samples of the German population conducted between 02/2021-04/2022. Associations between smoking status (current, long-term ex-, never) and three self-reported outcomes (corona infection status, symptom severity, and symptom duration) were analysed with regression models, adjusted for a range of potential confounding factors, including vaccination status in a sub-sample. We also ran sensitivity analyses. *Results:* 872 people reported an infection (5.4 % of 16,028). There was no relevant and statistically significant association between current smoking and long-term ex-smoking compared with never smoking regarding ever being infected with corona (aOR=1.02, 95 %CI=0.86–1.20 and aOR=1.03, 95 %CI=0.83–1.28, respectively), symptom severity (aOR=0.84, 95 %CI=0.59–1.20 and aOR=0.88, 95 %CI=0.55–1.38, respectively), and symptom duration (aβ)=-0.09 months, 95 %CI=-0.45–0.28 and aβ=0.002 months, 95 %CI=-0.48–0.48). Sensitivity analyses examining the interaction between survey wave and smoking status showed that the risk of an infection increased over time, and this increase was higher in current smokers compared with never smokers. *Conclusions:* In the general German population smokers appear to be as likely to acquire a corona infection as long-term ex- and never smokers.

Keywords: COVID-19, SARS-CoV-2, tobacco smoking, disease severity, disease duration, vaccination, population survey

Zusammenhang zwischen Tabakrauchstatus und selbst-berichteter SARS-CoV-2/COVID-19-Infektion, Krankheitsschwere und -dauer in der Allgemeinbevölkerung Deutschlands

Zusammenfassung: *Einführung:* Es gibt widersprüchliche Theorien darüber, welche Rolle Tabakrauchen und/oder Nikotin bei der Anfälligkeit für eine Infektion mit dem schweren akuten respiratorischen Syndrom Coronavirus 2 (SARS-CoV-2) und der Coronavirus-Krankheit 2019 (COVID-19) spielen. Unser Ziel war es, in der Allgemeinbevölkerung Deutschlands den Zusammenhang zwischen dem Tabakrauchstatus und der selbst-berichteten SARS-CoV-2-Infektion, dem Schweregrad der COVID-19-Symptome und der Symptomdauer zu untersuchen. *Methodik:* Querschnittliche Haushaltsbefragung mit persönlich-mündlichen Interviews bei repräsentativen Stichproben der in Deutschland lebenden Bevölkerung, durchgeführt zwischen Februar 2021 und April 2022. Die Zusammenhänge zwischen dem Rauchstatus (aktuelle_r Raucher_in, langjährige_r Ex-Raucher_in und Nie-Raucher_in) und drei selbstberichteten Endpunkten (Corona-Infektionsstatus, Schweregrad der Corona-Symptome bei Infizierten und Dauer der Corona-Symptome bei Personen mit Corona-Symptomen) wurden mit multivariablen Regressionsmodellen analysiert, adjustiert für eine Reihe potenzieller Störfaktoren, einschließlich des Impfstatus in einer Unterstichprobe. Wir führten zudem Sensitivitätsanalysen durch. *Ergebnisse:* Insgesamt meldeten 872 Personen eine Corona-Infektion (5.4 % von 16.028). Es bestand kein relevanter und statistisch signifikanter Zusammenhang zwischen aktuellem Rauchen und langfristigem Ex-Rauchen im Vergleich zu Nie-Rauchen im Hinblick auf eine jemals erworbene Corona-Infektion (adustierte Odds Ratio (aOR) = 1.02, 95 % Konfidenzintervall (95 %KI) = 0.86–1.20 bzw. aOR=1.03, 95 %KI=0.83–1.28), Schweregrad der Corona-Symptome (aOR=0.84, 95 %KI=0.59–1.20 bzw. aOR=0.88, 95 %KI=0.55–1.38) und Dauer der Corona-Symptome (bereinigter β-Koeffizient (aβ)=-0.09 Monate, 95 %CI=-0.45–0.28 und aβ=0.002 Monate, 95 %KI=-0.48–0.48).

Sensitivitätsanalysen, die die Interaktion zwischen der Erhebungswelle (auf einer metrischen Skala) und dem Raucherstatus untersuchten, zeigten, dass das Risiko einer Infektion im Laufe der Zeit anstieg, und dieser Anstieg war bei aktuellen Rauchern höher als bei Nie-Rauchern. *Schlussfolgerung:* In der deutschen Allgemeinbevölkerung scheinen Raucher_innen ebenso häufig an einer Corona-Infektion zu erkranken wie Langzeit-Ex-Raucher_innen und Nie-Raucher_innen.

Schlüsselwörter: COVID-19, SARS-CoV-2, Tabakrauchen, Krankheitsschwere, Krankheitsdauer, Impfung, Bevölkerungsumfrage

Background

The Coronavirus disease 2019 (COVID-19) is a contagious respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus (World Health Organization, 2021). Due to its high transmissibility, governments worldwide issued various behavioural restrictions such as periodic lockdowns to reduce the spread of the virus and to avoid overloading hospital systems from February 2020 (Taylor, 2021). About a year into the pandemic, on December 27, 2020, Germany's vaccine program was rolled out, thus providing effective protection against severe disease and mortality, especially to those at high risk (e.g., older adults, men, individuals with comorbidities). While the COVID-19 vaccine campaign made its way slowly through the German population in 2021, surges of infections erupted due to the Delta variant of the SARS-CoV-2 virus. As of October 3rd, 2023, there have been an estimated total of 38 million cases and 168,935 deaths due to COVID-19 in Germany (John Hopkins University & Medicine, 2023).

There have been conflicting theories about the role tobacco smoking and/or nicotine plays in the susceptibility of COVID-19 infection, disease severity, and symptoms. One of the defining features of the SARS-CoV-2 virus is its spike protein, which is involved in receptor recognition, viral attachment, and entry into host cells via the host cell receptor angiotensin-converting enzyme 2 (ACE-2) (Huang et al., 2020). In some studies, active cigarette smoking has been found to upregulate ACE-2 expression, suggesting that smokers may be at an increased risk of a SARS-CoV-2 infection (Leung et al., 2020; Smith et al., 2020). However, reduced receptor levels in smokers have also been reported (Oakes et al., 2018). It has also been suggested that nicotine competes with SARS-CoV-2 for the nicotinic acetylcholine receptor, which acts as a co-receptor for viral cell entry (Farsalinos, Barbouni et al., 2020; Farsalinos, Niaura et al., 2020; Grundy et al., 2020). Furthermore, behavioural factors might play a role such as risk-reducing behaviour (e.g., meeting other people rather outdoors than indoors, or meeting less frequently) in smokers with pre-existing diseases (e.g., pulmonary or heart diseases) out of a fear of respiratory complications of COVID-19 (Richard et al., 2022; Wagner et al., 2021).

Current evidence about smoking and the risk of corona infection and disease outcomes includes a large living evidence review of over 500 studies from around the globe by Simons et al. (Simons et al., 2021). Findings from their unadjusted meta-analyses showed current smokers compared to never smokers were at a decreased risk of SARS-CoV-2 infection (Relative risk [RR] = 0.67, credible interval [CrI]= 0.60–0.75); and among hospitalised patients, current smokers compared to never smokers had an increased risk of greater COVID-19 severity (RR=1.3, CrI=1.01–1.71) (Simons et al., 2021). Mendelian randomization studies have further supported findings that smoking increases the risk of severe COVID-19 (Clift et al., 2022; Yeung et al., 2022).

Lacking in the literature are studies with random or representative population samples. The majority of studies have been conducted in hospital settings and with selected populations. The few high quality population studies did not primarily focus on the association between smoking and SARS-CoV-2 / COVID-19 (Barchuk et al., 2021; Carrat et al., 2021; Gornyk et al., 2021; Merkely et al., 2020; Radon et al., 2021; Richard et al., 2022; Wagner et al., 2021). Subsequent methodological limitations include incomplete data regarding smoking behaviour (in particular the distinction between recent vs. long-term ex-smoking), a lack of or incomplete adjustment for confounding factors, samples that did not capture the entire population or focused on only patient populations, and not capturing or reporting on asymptomatic infections.

The present study therefore aimed to add to the existing evidence by addressing the following research questions using self-reported data from a representative survey of the German population: (1) In the general German population aged 14+ years, compared with never smoking is (a) current and (b) former smoking associated with an increased risk of SARS-CoV-2 infection? (2) In people with a SARS-CoV-2 infection, compared with never smoking is (a) current and (b) former smoking associated with an increased risk of more severe COVID-19 symptoms? (3) In people who have COVID-19 with symptoms, compared with never smoking is (a) current and (b) former smoking associated with an increased risk of longer COVID-19 symptom duration? Evidence about the role of tobacco smoking and/or nicotine is potentially useful for future efforts of disease prevention and risk communication.

Methods

We conducted a cross-sectional analysis using data from the German Study on Tobacco Use (DEBRA: "Deutsche Befragung zum Rauchverhalten"): an ongoing representative household survey on tobacco use in the German population (Kastaun et al., 2017). The DEBRA study collects bimonthly data from computer-assisted face-to-face household interviews in a sample of approximately 2,000 persons aged 14+ per wave. Respondents were selected by using a dual frame design: a composition of random stratified sampling (50 % of the sample) and quota sampling (50 % of the sample). Details regarding this sampling design have been described in detail elsewhere (https://osf.io/e2nqr/). Data collection on COVID-19 infections and symptoms started in wave 28 (February/March 2021) of the DEBRA study and continued until wave 35 (March/April 2022). Additional data on corona vaccination were collected in waves 34 (January/February 2022) and 35. Respondents were not reimbursed for participation. The DEBRA study has been registered at the German Clinical Trials Register (registration numbers DRKS00011322, DRKS00017157, and DRKS00028054). We published a detailed study protocol a priori to analysing the data (https://osf.io/pzrv3).

Outcomes

We measured our first outcome – corona infection – by asking whether a person had ever been infected with the corona virus: "Have you ever been tested for the corona virus by healthcare personnel (no self-test)?" Response options: (1) Yes, and I have tested positive at least once; (2) Yes, but I have always tested negative; (3) Yes, but I am still waiting for the result; (4) No, I have never been tested for the corona virus; (5) I don't know if I have ever been tested for the corona virus; and (6) no response. We relied on self-report; the infection status was not verified by a written report from a laboratory or test station. The variable was dichotomised into infection (response 1) and no infection (responses 2–5). For a sensitivity analysis, the variable was dichotomised into infection (response 1) and no infection (responses 2–4), thus excluding also the "I don't know if I have ever been tested" group.

In the subgroup of persons who had ever been infected with the corona virus (i.e., question 1, response 1), we measured our second outcome – corona symptom severity – by asking. "The main symptoms of the corona virus are, for example, fever over 38 degrees; a new, persistent cough or a cold; head and limb pain; or disturbed smell and taste. When you think about it, how severe were the symptoms of your corona disease?" Response options: (1) I had no symptoms or the test result was probably wrong; (2) I only had mild symptoms; (3) I had severe symptoms, but could cure myself at home; (4) I had severe symptoms and had to get treatment in a hospital; (5) In the hospital I needed intensive care treatment or had to be intubated; (6) no response. The variable was dichotomised into low symptom severity (responses 1–2) and high symptom severity (responses 3–5). For a sensitivity analysis, the variable was dichotomised into no hospitalisation (responses 1–3) and hospitalisation (responses 4–5).

In a further subgroup of persons with corona symptoms (i.e., question 2, responses 2–5), we measured our third outcome – corona symptom duration – by asking the following two questions: "How long ago was your corona disease?" Response options: (1) In the past month; (2) 1–3 months; (3) 3–6 months; (4) 6–9 months; (5) 9–12 months; (6) longer than 12 months; and (7) no response. "How long did the complaints of your corona disease last approximately?" Response options: (1) until today; (2) 1 month; (3) 1–3 months; (4) 3–6 months; (5) 6–9 months; (6) 9–12 months; (7) longer than 12 months; and (8) no response. These two variables were combined and invalid combinations corrected to estimate the symptom duration on a metric scale ranging from 0.5 to 12 months (details see Electronic Supplementary Material [ESM] 1).

Exposures

We measured our exposures of interest by asking: "Which of the following applies to you best? Please note that smoking means smoking tobacco and not electronic cigarettes or heated tobacco products." Response options: (1) I smoke cigarettes every day; (2) I smoke cigarettes, but not every day; (3) I do not smoke cigarettes at all, but I do smoke tobacco of some kind (e.g., pipe or cigar); (4) I have stopped smoking completely in the last year; (5) I stopped smoking completely more than a year ago; (6) I have never been a smoker (i.e., smoked for a year or more); and (7) no response.

We defined current tobacco smoking by responses 1, 2 or 3, long-term ex-smoking by responding 5, and never smoking by responding 6. Recent ex-smokers (response 4; 1.0 % of the total sample) were excluded from the analyses to avoid the risk of misclassification (i.e., the possibility that smokers stop smoking due to their corona symptoms).

Potential Confounding Variables

We included the following potential confounding variables from the DEBRA database in our adjusted analyses (see ESM 2 for causal diagrams): years of age (continuous vari-

able), sex (binary: female, male), migration background (binary: at least one of the parents born abroad, none), number of persons in the household aged 18+ years, number of persons in the household aged <18 years, monthly net household income per person in the household (continuous variable), educational attainment (categorical: low, middle, high), region of living (binary: rural, urban), and wave of the survey (categorical: DEBRA wave 28–35).

An important aspect of corona infection and symptoms is vaccination against the corona virus. The vaccination program in Germany started at the end of the year 2020, but it took until mid-June 2021 until approximately half the population had received at least one vaccination dose (https://impfdashboard.de). We only started to collect data on the vaccination status (i.e., having received at least one vaccination) of the respondents to the DEBRA survey in wave 34 (January/February 2022; also here, we relied on self-report) and were therefore unable to adjust our main analyses for this factor. However, we conducted a sensitivity analysis which takes this aspect into account (see below).

Statistical Analyses

We pre-registered our statistical analysis plan in our study protocol (https://osf.io/pzrv3). Our statistical analyses included 3 regression models based on a complete cases dataset (people with missing data excluded): First, to analyse the association between smoking status and corona infection (research question 1), we used a multivariable logistic regression model with corona infection (infection vs. no infection) as the dependent variable and smoking (current smoking, long-term ex-smoking vs. never smoking = reference) as the main independent variable. Second, to analyse the association between smoking status and corona symptom severity (research question 2), we selected the sub-sample of people who ever had a corona infection and used a multivariable logistic regression model with corona symptom severity (high vs. low symptom severity) as the dependent variable and smoking (current smoking, long-term ex-smoking vs. never smoking = reference) as the main independent variable. Third, to analyse the association between smoking status and corona symptom duration (research question 3), we selected the sub-sample of people who ever had a corona infection with symptoms and used a multivariable linear regression model with corona symptom duration (metric, ranging from 0.5 to 12 months) as the dependent variable and smoking (current smoking, long-term ex-smoking vs. never smoking = reference) as the main independent variable. All models were adjusted for the above mentioned potentially confounding factors. We used IBM® SPSS Statistics Version 27 for the analyses.

We had planned the following sensitivity analyses: (1) a repetition of analyses 1–2 with a differently coded dependent variable (see outcomes section above); (2) a repetition of analyses 1–3 in a sample restricted to waves in which only a minority of the population had been vaccinated (waves 28–30; February/March 2021 to May/June 2021); and (3) a repetition of analyses 1–3 in a sample restricted to waves in which we collected data on the vaccination status of the respondents (wave 34–35 (January/February 2022 to March/April 2022).

Results

A total of 16,361 people were interviewed in the period between 18 February 2021 and 5 April 2022 (waves 28–35 of the DEBRA study), of which 16,028 were current smoker, long-term ex-smoker or never smoker who responded to the question regarding corona infection (79/16,107=0.5% did not respond). The characteristics of the study population are shown in Table 1. Current smokers were somewhat younger and more frequently male and with a migration status. Furthermore, the rate of vaccination against SARS-CoV-2 (only measured in waves 34–35) was lower in current smokers (89.2%) than in long-term ex-smokers (93.3%) and never smokers (93.9%).

A total of 872 people reported ever being infected with corona (5.4%; Table 1 and ESM 3). A post-hoc ancillary analysis assessing the validity of this self-report showed that our estimated infection rates at the time points of the various surveys waves were comparable to the official infection rates from the Robert Koch Institute (see ESM 4). Among the 872 people with an infection, 610 (70.0%) reported a low symptom severity (including n=148 without symptoms; Table 1 and ESM 5). Among the 724 people with an infection and with symptoms of any degree, 77 (10.6%) reported a symptom duration of 4.5 months or longer (Table 1 and ESM 1).

Our first regression model included 14,730 people after 1,298 (8.1% of 16,028) with missing data on one or more of the potentially confounding factors included in the model had been excluded. The odds of an infection showed no relevant or statistically significant difference between current (adjusted odds ratio (aOR) = 1.02, 95% confidence interval (95%CI) = 0.86–1.20) and long-term ex-smokers (aOR=1.03, 95%CI=0.83–1.28) compared with never smokers (Table 2).

Our second regression model, in the sub-sample of people who ever had a corona infection, included 800 people after 72 (8.2% of 872) with missing data had been excluded. Both current (aOR=0.84, 95%CI=0.59–1.20) and long-term ex-smokers (aOR=0.88, 95%CI=0.55–1.38) had a

lower but statistically non-significant odds of high symptom severity compared with never smokers (Table 2).

Our third regression model, in the sub-sample of people who ever had a corona infection with symptoms included 626 cases. A total of 98 people (13.5% of 724) with missing data had been excluded. The symptom duration between current smokers (adjusted β-coefficient (aβ)=-0.09, 95%CI=-0.45–0.28) and long-term ex-smokers (aβ=0.002, 95%CI=-0.48–0.48) showed no relevant difference from never smokers (Table 2).

Our a priori planned sensitivity analyses yielded partly different effect estimates, but none of the associations were statistically significant (ESM 6, 7, 8). Regarding our first outcome, our sensitivity analysis with restriction to waves 28–30 in which only a minority of the population had been vaccinated showed a lower but statistically non-significant odds of an infection both in current (aOR=0.86, 95%CI=0.57–1.28) and in long-term ex-smokers (aOR=0.83, 95%CI=0.51–1.37) compared with never smokers (ESM 7). Our sensitivity analysis with restriction to waves 34–35 which included additional adjustment for the vaccination status of the respondents showed a higher but statistically non-significant odds of an infection both in current (aOR=1.06, 95%CI=0.84–1.33) and in long-term ex-smokers (aOR=1.10, 95%CI=0.81–1.50) compared with never smokers (ESM 8). This led us to perform a post-hoc ancillary analysis using all data (waves 28–35) which showed a statistically significant interaction between wave of the survey (on a metric scale) and smoking status: the risk of an infection increased over time, but this increase was higher in current smokers compared with never smokers (aOR=1.10, 95%CI=1.01–1.19: ESM 9). Subsequent analyses of the effect of time, stratified by smoking status, showed the following increases in the risk of an infection with increasing wave of the survey: aOR=1.48 (95%CI=1.39–1.59) in current smokers, aOR=1.37 (95%CI=1.25–1.50) in long-term ex-smokers, and aOR=1.36 (95%CI=1.29–1.43) in never smokers.

Discussion

Our study using representative data from the German population collected in the period between February 2021 and April 2022 showed no relevant and statistically significant differences in self-reported corona infections, corona symptom severity, and corona symptom duration between current smokers, long-term ex-smokers, and never smokers.

Table 1. Characteristics of the study population by smoking status

Characteristic		Current smoker (n=5,242)	Long-term ex-smoker (n=2,731)	Never smoker (n=8,134)
Age, years: mean (SD)		47.7 (16.1)	58.1 (16.3)	51.5 (20.3)
Female sex		46.4 (2,420)	43.2 (1,175)	58.7 (4,744)
Migration background		15.9 (788)	12.9 (327)	14.2 (1,092)
No. people in household >18 years: mean (SD)		1.8 (0.8)	1.8 (0.7)	1.8 (0.8)
No. people in household <18 years: mean (SD)		0.4 (0.8)	0.3 (0.7)	0.4 (0.8)
Monthly household income p. p. in €1000: mean (SD)		1.6 (0.9)	1.8 (0.8)	1.7 (0.9)
Educational attainment	low	33.3 (1,712)	29.7 (807)	27.7 (2,130)
	middle	43.6 (2,243)	39.0 (1,057)	34.8 (2,682)
	high	23.1 (1,185)	31.1 (849)	37.5 (2,886)
Rural region of living		39.8 (2,078)	34.2 (932)	35.1 (2,836)
Ever infected with SARS-CoV-2		6.1 (317)	4.9 (134)	5.2 (421)
COVID-19 without or with mild symptoms†		73.2 (230)	70.1 (94)	68.1 (286)
COVID-19 symptom duration >4.5 months‡		9.2 (23)	13.1 (14)	12.7 (40)
SARS-CoV-2 vaccination received¥		89.2 (1,282)	93.3 (586)	93.9 (1,848)

Notes. Data presented as column percentage (number), unless stated otherwise. †In people ever infected with SARS-CoV-2 (314 current smokers, 134 long-term ex-smokers, 420 never smokers, 4 missings). ‡In people with at least mild symptoms (250 current smokers, 107 long-term ex-smokers, 315 never smokers, 52 missings). ¥Data on vaccination status only collected in 2 waves of the survey (waves 34–35: 1,437 current smokers, 628 long-term ex-smokers, 1,969 never smokers, 75 missings).

Table 2. Associations between smoking status and corona infection, corona symptom severity, and corona symptom duration, adjusted for potential confounders

Smoking status	Infection yes vs. no infection aOR (95 %CI) n=14,730	Symptom severity high vs. low aOR (95 %CI) n=800	Symptom duration in months aβ (95 %CI) n=626
Current	1.02 (0.86–1.20)	0.84 (0.59–1.20)	-0.09 (-0.45–0.28)
Long-term ex-smoking	1.03 (0.83–1.28)	0.88 (0.55–1.38)	0.002 (-0.48–0.48)
Never smoking (reference)	1	1	1

Notes. aOR = adjusted odds ratio. aβ = adjusted β-coefficient of linear regression model. 95 %CI = 95 % confidence interval around OR or β. OR and β adjusted for: age, sex, migration background, people in household 18+ years, people in household aged <18 years, income, education, region of living, and wave of the survey.

Only few population-based studies have investigated the association between smoking status and SARS-CoV-2 infection so far. These studies were conducted in Germany (Gornyk et al., 2021; Radon et al., 2021; Wagner et al., 2021), France (Carrat et al., 2021), Russia (Barchuk et al., 2021), and Switzerland (Richard et al., 2022) in a period between April 2020 and February 2021. All studies used SARS-CoV-2 antibodies from blood samples as outcome measure and consistently reported lower seropositivity in current smokers compared with never smokers. We used self-reported SARS-CoV-2 infection detected with a positive test by healthcare personnel as an outcome measure and found that smokers were at the same odds of an infection as never smokers. Such tests are usually rapid antigen tests aimed at detecting SARS-CoV-2 virus load. Hence, it may be that smokers are just as likely to acquire a SARS-CoV-2 infection (measurable with an antigen test) but are less likely to produce sufficient antibodies after an infection which then results in a lower seropositivity. This may be one explanation why studies using antibodies as the outcome measure reported lower infection rates in smokers. This is supported by the consistent finding from various vaccination studies that smokers show lower SARS-CoV-2 antibody titres compared with non-smokers (Ferrara et al., 2022; Herzberg et al., 2022; Swartz et al., 2023; Toda et al., 2022; Tsatsakis et al., 2021; Uysal et al., 2022; Watanabe et al., 2022; Yamamoto et al., 2022). However, in a series of planned and unplanned sensitivity analyses, there was some indication (albeit non-significant) that current compared with never smokers had reduced odds of infection when restricting the analyses to the survey waves prior to widespread vaccination – which is consistent with findings from a recent living review of >500 observational studies (Simons et al., 2021). In addition, a significant interaction between survey wave and smoking status was observed, with the risk of infection increasing over time across all levels of smoking status but with the increase being more pronounced in current compared with never smokers. This could be interpreted to suggest that the initially observed negative association between current (compared with never) smoking and infection has attenuated over the course of the pandemic due to mass infection and/or current smokers being less likely to produce a sufficient immune response following vaccination. Furthermore, the pronounced increase in infection rate in current smokers may be due to a lower vaccination rate in this very group.

We also did not find a statistical significant association between smoking status and corona symptom severity. Two large-scale observational and Mendelian randomisation studies reported an increased risk of hospitalisation and COVID-19-related mortality in current smokers compared with never smokers (Clift et al., 2022; Yeung et al., 2022). Previous studies conducted in hospitalised patients also found an increased risk of greater COVID-19 severity among current smokers compared with never smokers (Simons et al., 2021). Our study, however, was based on a general population sample in which the majority of people with a self-reported infection (70.1 % of 893) reported no or mild symptoms. Only 25 people (2.8 %) reported treatment in a hospital. Hence, our sample size was probably too low to detect any meaningful differences. Furthermore, the highest degree of corona symptom severity we were able to measure with our survey was intensive care treatment in hospital, and this only in those who recovered in such a way that allows living at home and responding to an interview survey. If smokers are more likely to being hospitalised and to die from COVID-19 than never smokers, as the above-mentioned studies suggest, our analysis of the association between smoking status and corona symptom severity might have been biased due to selection.

There is very little evidence about the association between smoking status and corona symptom duration in the general population. In our sample, 10.6 % reported a symptom duration of 4.5 months or longer, which can be regarded as indicative of long COVID (Shah et al., 2021). Longitudinal population studies from the UK and the US reported prevalence rates for long COVID between 10–38 % (Whitaker et al., 2022; Wu et al., 2022). The UK study

found an increased risk of persistent symptoms in current smokers compared with non-current smokers (Whitaker et al., 2022). On the contrary, the US study, which also took pre-infection symptoms and existing health conditions at baseline into account, did not find an increased risk in current smokers (Wu et al., 2022). Hence, current smoking may not be a risk factor for corona symptom duration, or at least less important than other risk factors such as obesity (Whitaker et al., 2022; Wu et al., 2022).

Limitations and Strengths

Our study has several limitations. First, our study had a cross-sectional design which limits the ability to assess temporal associations between exposures and outcomes. For example, it is possible that a corona infection with symptoms affects smoking behaviour, in particular that it triggers smoking cessation. We tried to limit this risk of bias by excluding recent ex-smokers (those who stopped smoking <12 months) from our analyses. Second, our outcome measures were prone to bias because they relied on self-report and recall of corona infections that occurred in the past and corona symptoms, most of which are unspecific, although we have no reason to assume that recall differs by smoking status. Third, for the measurement of our outcome corona infection, we asked for a positive test by healthcare personnel in order to differentiate such a test from self-tests at home which are more prone to errors in handling and interpretation. However, there is a chance of misinterpretation because tests are often performed at test stations by persons who may or may not be healthcare professionals. Also, we did not have any information on the type of tests used, which would impact sensitivity and specificity of viral detection. Fourth, our measurement of exposure was restricted to smoked tobacco and did not include the use of other nicotine products such as e-cigarettes or heated tobacco products which may also have adverse effects on respiratory health. Finally, some relevant potential confounding variables were not measured such as comorbidities, place of work (home working), and key worker status, and vaccination status was not measured during the entire observational period. Our sensitivity analyses with data restricted to waves with information on vaccination status yielded similar results as our main analyses, though. Nevertheless, residual confounding may have occurred. Strengths of our study include the use of a representative sample of the general population (as indicated by the self-reported infection rates which are comparable with official infection rates from the Robert Koch Institute during most of the study period; see Figure S2); however, given the dynamic nature of a communicable disease like SARS-CoV-2, which moves through the population at varying rates depending on the number of infections, susceptible individuals and recovered individuals at each time point, the degree of representativeness of our survey with respect to SARS-CoV-2 infection dynamics remains unknown. Another strength of the study includes having followed a well-planned and a priori published analysis plan including well-founded adjustment for various important confounders.

Conclusion and Recommendations

Based on our study findings and in light of previous research we conclude that – in the general German population – smokers appear to be just as likely to acquire a corona infection as long-term ex-smokers and never smokers. The majority of participants experienced mild symptoms and symptoms that last less than three months. Our findings regarding the association between smoking status and symptom severity and duration are inconclusive due to methodological limitations. More longitudinal studies in representative samples of the population and with extended measurement of prognostic factors of corona disease progression are needed to disentangle the complex relationships with smoking.

Implications

- Current tobacco smokers appear to be just as likely to acquire a corona infection as long-term ex-smokers and never smokers.
- The finding from previous studies reporting a reduced risk of corona infection in current smokers based on SARS-CoV-2 antibodies from blood samples as outcome measure may have been biased. One explanation could be that smokers are less likely to produce sufficient antibodies after an infection which then results in a lower seropositivity.
- The majority of smokers with a corona infection experiences mild symptoms and symptoms that last less than three months.

Electronic Supplementary Material

The electronic supplementary material (ESM) is available with the online version of the article at https://doi.org/10.1024/0939-5911/a000858

ESM 1. Responses to the outcome corona symptom duration in subsample of people with a corona infection and symptoms of any degree (Table)
ESM 2. Causal diagrams indicating the hypothetical associations between exposure, the outcomes and potential confounding factors (Figures)
ESM 3. Responses to the outcome corona infection in total sample (Table)
ESM 4. Weighted lifetime prevalence of corona infection rates at different time points of the DEBRA waves estimated with DEBRA data compared with official cumulative corona infection rates from the Robert Koch Institute (Figure)
ESM 5. Responses to the outcome corona symptom severity in subsample of people with a corona infection (Table)
ESM 6. Sensitivity analyses of the associations between smoking status and corona infection and corona symptom severity, adjusted for potential confounders (Table)
ESM 7. Sensitivity analyses (restriction to waves 28–30 in which only a minority of the population had been vaccinated) of the associations between smoking status and corona infection, corona symptom severity, and corona symptom duration, adjusted for potential confounders (Table)
ESM 8. Sensitivity analyses of the associations between smoking status and corona infection, corona symptom severity, and corona symptom duration, adjusted for potential confounders (Table)
ESM 9. Post-hoc ancillary sensitivity analysis of the associations between smoking status and corona infection, adjusted for potential confounders (Table)

References

Barchuk, A., Skougarevskiy, D., Titaev, K., Shirokov, D., Raskina, Y., Novkunkskaya, A., Talantov, P., Isaev, A., Pomerantseva, E., Zhikrivetskaya, S., Barabanova, L., & Volkov, V. (2021). Seroprevalence of SARS-CoV-2 antibodies in Saint Petersburg, Russia: A population-based study. *Scientific Reports, 11*(1), Article 12930. https://doi.org/10.1038/s41598-021-92206-y

Carrat, F., de Lamballerie, X., Rahib, D., Blanché, H., Lapidus, N., Artaud, F., Kab, S., Renuy, A., Szabo de Edeleny, F., Meyer, L., Lydié, N., Charles, M.-A., Ancel, P.-Y., Jusot, F., Rouquette, A., Priet, S., Villarroel,P.M.S., Fourié, T., Lusivika-Nzinga, C., … Zins, M. (2021). Antibody status and cumulative incidence of SARS-CoV-2 infection among adults in three regions of France following the first lockdown and associated risk factors: A multicohort study. *International Journal of Epidemiology, 50*(5), 1458–1472. https://doi.org/10.1093/ije/dyab110

Clift, A.K., von Ende, A., San Tan, P., Sallis, H.M., Lindson, N., Coupland, C.A.C., Munafò, M.R., Aveyard, P., Hippisley-Cox, J., & Hopewell, J.C. (2022). Smoking and COVID-19 outcomes: An observational and Mendelian randomisation study using the UK Biobank cohort. *Thorax, 77*(1), 65–73. https://doi.org/10.1136/thoraxjnl-2021-217080

Farsalinos, K., Barbouni, A., Poulas, K., Polosa, R., Caponnetto, P., & Niaura, R. (2020). Current smoking, former smoking, and adverse outcome among hospitalized COVID-19 patients: A systematic review and meta-analysis. *Therapeutic Advances in Chronic Disease, 11*, Article 2040622320935765. https://doi.org/10.1177/2040622320935765

Farsalinos, K., Niaura, R., Le Houezec, J., Barbouni, A., Tsatsakis, A., Kouretas, D., Vantarakis, A., & Poulas, K. (2020). Nicotine and SARS-CoV-2: COVID-19 may be a disease of the nicotinic cholinergic system. *Toxicology Reports, 7*, 658–663. https://doi.org/10.1016/j.toxrep.2020.04.012

Ferrara, P., Ponticelli, D., Agüero, F., Caci, G., Vitale, A., Borrelli, M., Schiavone, B., Antonazzo, I.C., Mantovani, L.G., Tomaselli, V., & Polosa, R. (2022). Does smoking have an impact on the immunological response to COVID-19 vaccines? Evidence from the VASCO study and need for further studies. *Public Health, 203*, 97–99. https://doi.org/10.1016/j.puhe.2021.12.013

Gornyk, D., Harries, M., Glöckner, S., Strengert, M., Kerrinnes, T., Heise, J.K., Maaß, H., Ortmann, J., Kessel, B., Kemmling, Y., Lange, B., & Krause, G. (2021). SARS-CoV-2 seroprevalence in Germany. *Deutsches Ärzteblatt International, 118*(48), 824–831. https://doi.org/10.3238/arztebl.m2021.0364

Grundy, E.J., Suddek, T., Filippidis, F.T., Majeed, A., & Coronini-Cronberg, S. (2020). Smoking, SARS-CoV-2 and COVID-19: A review of reviews considering implications for public health policy and practice. *Tobacco Induced Diseases, 18*, Article 58. https://doi.org/10.18332/tid/124788

Herzberg, J., Vollmer, T., Fischer, B., Becher, H., Becker, A.-K., Honarpisheh, H., Guraya, S.Y., Strate, T., &. Knabbe, C. (2022). SARS-CoV-2-antibody response in health care workers after vaccination or natural infection in a longitudinal observational study. *Vaccine, 40*(2), 206–212. https://doi.org/10.1016/j.vaccine.2021.11.081

Huang, Y., Yang, C., Xu, X.-f., Xu, W., & Liu, S.-w. (2020). Structural and functional properties of SARS-CoV-2 spike protein: Potential antivirus drug development for COVID-19. *Acta Pharmacologica Sinica, 41*(9), 1141–1149. https://doi.org/10.1038/s41401-020-0485-4

John Hopkins University & Medicine. (2023). *Coronavirus resource center*. https://coronavirus.jhu.edu/region/germany

Kastaun, S., Brown, J., Brose, L.S., Ratschen, E., Raupach, T., Nowak, D., Cholmakow-Bodechtel, C., Shahab, L., West, R., & Kotz, D. (2017). Study protocol of the German Study on Tobacco Use (DEBRA): A national household survey of smoking behaviour and cessation. *BMC Public Health, 17*(1), Article 378. https://doi.org/10.1186/s12889-017-4328-2

Leung, J.M., Yang, C.X., Tam, A., Shaipanich, T., Hackett, T.-L., Singhera, G.K., Dorscheid, D.R., & Sin, D.D. (2020). ACE-2 expression in the small airway epithelia of smokers and COPD patients: Implications for COVID-19. *European Respiratory Journal, 55*(5), Article 2000688. https://doi.org/10.1183/13993003.00688-2020

Merkely, B., Szabó, A.J., Kosztin, A., Berényi, E., Sebestyén, A., Lengyel, C., Merkely, G., Karády, J., Várkonyi; I., Papp, C., Miseta, A., Betlehem, J., Burián, K., Csóka, I., Vásárhelyi, B., Ludwig, E., Prinz, G., Sinkó, J., Hankó, B., … Hungarian CoronaVirus-Epidemiological Research investigators. (2020). Novel coronavirus epidemic in the Hungarian population: A cross-sectional nationwide survey to support the exit policy in Hungary. *GeroScience, 42*(4), 1063–1074. https://doi.org/10.1007/s11357-020-00226-9

Oakes, J.M., Fuchs, R.M., Gardner, J.D., Lazartigues, E., & Yue, X. (2018). Nicotine and the renin-angiotensin system. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 315*(5), R895-R906. https://doi.org/10.1152/ajpregu.00099.2018

Radon, K., Bakuli, A., Pütz, P., Le Gleut, R., Guggenbuehl Noller, J.M., Olbrich, L., Saathoff, E., Garí, M., Schälte, Y., Frahnow, T., Wölfel, R., Pritsch, M., Rothe, C., Pletschette, M., Rubio-Acero, R., Beyerl, J., Metaxa, D., Forster, F., Thiel, V., … KoCo19 study group. (2021). From first to second wave: Follow-up of the prospective COVID-19 cohort (KoCo19) in Munich (Germany). *BMC Infectious Diseases, 21*(1), Article 925. https://doi.org/10.1186/s12879-021-06589-4

Richard, A., Wisniak, A., Perez-Saez, J., Garrison-Desany, H., Petrovic, D., Piumatti, G., Baysson, H., Picazio, A., Pennacchio, F., De Ridder, D., Chappuis, F., Vuilleumier, N., Low, N., Hurst, S., Eckerle, I., Flahault, A., Kaiser, L., Azman, A.S., Guessous, I., & Stringhini, S. (2022). Seroprevalence of anti-SARS-CoV-2 IgG antibodies, risk factors for infection and associated symptoms in Geneva, Switzerland: A population-based study. *Scandinavian Journal of Public Health, 50*(1), 124–135. https://doi.org/10.1177/14034948211048050

Shah, W., Hillman, T., Playford, E.D., & Hishmeh, L. (2021). Managing the long term effects of Covid-19: Summary of NICE, SIGN, and RCGP rapid guideline. *BMJ, 372*, Article n136. https://doi.org/10.1136/bmj.n136

Simons, D., Shahab, L., Brown, J., & Perski, O. (2021). The association of smoking status with SARS-CoV-2 infection, hospitalization and mortality from COVID-19: A living rapid evidence review with Bayesian meta-analyses (Version 7). *Addiction, 116*(6), 1319–1368. https://doi.org/10.1111/add.15276

Smith, J.C., Sausville, E.L., Girish, V., Yuan, M.L., Vasudevan, A., John, K.M., & Sheltzer, J.M. (2020). Cigarette smoke exposure and inflammatory signaling increase the expression of the SARS-CoV-2 receptor ACE2 in the respiratory tract. *Developmental Cell, 53*(5), 514–529. e513. https://doi.org/10.1016/j.devcel.2020.05.012

Swartz, M.D., DeSantis, S.M., Yaseen, A., Brito, F.A., Valerio-Shewmaker, M.A., Messiah, S.E., Leon-Novelo, L.G., Kohl, H.W., Pinzon-Gomez, C.L., Hao, T., Zhang, S., Talebi, Y., Yoo, J., Ross, J.R., Gonzalez, M.O., Wu, L., Kelder, S.H., Silberman, M., Tuzo, S., … Boerwinkle, E. (2023). Antibody duration after infection from SARS-CoV-2 in the Texas Coronavirus Antibody Response Survey. *The Journal of Infectious Diseases, 227*(2), 193–201.https://doi.org/10.1093/infdis/jiac167

Taylor, D.B. (2021). *A timeline of the coronavirus pandemic.* https://www.nytimes.com/article/coronavirus-timeline.html

Toda, M., Yoshifuji, A., Kikuchi, K., Koinuma, M., Komatsu, M., Fujii, K., Kato, A., Kikuchi, T., Nakazawa, A., & Ryuzaki, M. (2022). Factors associated with SARS-CoV-2 antibody titers and prognosis of breakthrough infection in hemodialysis patients. *Clinical and Experimental Nephrology, 26*(6), 571–580. https://doi.org/10.1007/s10157-022-02188-y

Tsatsakis, A., Vakonaki, E., Tzatzarakis, M., Flamourakis, M., Nikolouzakis, T.K., Poulas, K., Papazoglou, G., Hatzidaki, E., Papanikolaou, N.C., Drakoulis, N., Iliaki, E., Goulielmos, G.N., Kallionakis, M., Lazopoulos, G., Kteniadakis, S., Alegkakis, A., Farsalinos, K., & Spandidos, D.A. (2021). Immune response (IgG) following full inoculation with BNT162b2 COVID-19 mRNA among healthcare professionals. *International Journal of Molecular Medicine , 48*(5), Article 200. https://doi.org/10.3892/ijmm.2021.5033

Uysal, E.B., Gümüş, S., Bektöre, B., Bozkurt, H., & Gözalan, A. (2022). Evaluation of antibody response after COVID-19 vaccination of healthcare workers. *Journal of Medical Virology, 94*(3), 1060–1066. https://doi.org/10.1002/jmv.27420

Wagner, R., Peterhoff, D., Beileke, S., Günther, F., Berr, M., Einhauser, S., Schütz, A., Niller, H.H., Steininger, P., Knöll, A., Tenbusch, M., Maier, C., Korn, K., Stark, K.J., Gessner, A., Burkhardt, R., Kabesch, M., Schedl, H., Küchenhoff, H., … Überla, K. (2021). Estimates and determinants of SARS-Cov-2 seroprevalence and infection fatality ratio using latent class analysis: The population-based Tirschenreuth Study in the hardest-hit German county in spring 2020. *Viruses, 13*(6), Article 1118.

Watanabe, M., Balena, A., Tuccinardi, D., Tozzi, R., Risi, R., Masi, D., Caputi, A., Rossetti, R., Spoltore, M.E., Filippi, V., Gangitano, E., Manfrini, S., Mariani, S., Lubrano, C., Lenzi, A., Mastroianni, C., & Gnessi, L. (2022). Central obesity, smoking habit, and hypertension are associated with lower antibody titres in response to COVID-19 mRNA vaccine. *Diabetes/Metabolism Research and Reviews, 38*(1), Article e3465. https://doi.org/10.1002/dmrr.3465

Whitaker, M., Elliott, J., Chadeau-Hyam, M., Riley, S., Darzi, A., Cooke, G., Ward, H., & Elliott, P. (2022). Persistent COVID-19 symptoms in a community study of 606,434 people in England. *Nature Communications , 13*(1), Article 1957. https://doi.org/10.1038/s41467-022-29521-z

World Health Organization. (2021). *Listings of WHO's response to COVID-19*. https://www.who.int/news/item/29-06-2020-covidtimeline

Wu, Q., Ailshire, J.A., & Crimmins, E.M. (2022). Long COVID and symptom trajectory in a representative sample of Americans in the first year of the pandemic. *Scietific Reports, 12*(1), Article 11647. https://doi.org/10.1038/s41598-022-15727-0

Yamamoto, S., Tanaka, A., Ohmagari, N., Yamaguchi, K., Ishitsuka, K., Morisaki, N., Kojima.M., Nishikimi, A., Tokuda, H., Inoue, M., Tanaka, S., Umezawa, J., Okubo, R., Nishimura, K., Konishi, M., Miyo, K., &. Mizoue, T. (2022). Use of heated tobacco products, moderate alcohol drinking, and anti-SARS-CoV-2 IgG antibody titers after BNT162b2 vaccination among Japanese healthcare workers. *Preventiv Medicine, 161*, Article 107123. https://doi.org/10.1016/j.ypmed.2022.107123

Yeung, S.L.A., Li, A.M., He, B.T., Kwok, K.O., & Schooling, C.M. (2022). Association of smoking, lung function and COPD in COVID-19 risk: A two-step Mendelian randomization study. *Addiction, 117*(7), 2027–2036. https://doi.org/10.1111/add.15852

History
Manuscript received: September 8, 2023
Manuscript accepted: January 31, 2024

Declaration of Competing Interests
DK, OP, KG, and SK have nothing to declare. JB has received unrestricted research funding to study smoking cessation from Pfizer and J&J, who manufacture smoking cessation medications.

Publication Ethics
This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Heinrich-Heine-University Düsseldorf (HHU 5386R).

Author Contributions
DK conceived the DEBRA study, conceptualised and drafted the analysis protocol, drafted the manuscript, and analysed and interpreted the data. SK coordinated the DEBRA study and helped conceptualising the data collection regarding corona outcomes. All named authors contributed substantially to the analysis protocol and the manuscript, and agreed on its final version.

Open Data
The data underlying this article will be shared on reasonable request to the corresponding author.

Funding
The DEBRA study was funded from 2016 to 2019 (waves 1–18) by the Ministry of Innovation, Science and Research of the German State of North Rhine–Westphalia (MIWF) in the context of the

"NRW Rückkehrprogramm" (the North Rhine–Westphalian post-doc return program). Since 2019 (wave 19 onwards), the study has been funded by the German Federal Ministry of Health (ZMVI1-2519DSM203, ZMI1-2521DSM209). Open access publication enabled by Heinrich Heine University Duesseldorf.

ORCID
Daniel Kotz
https://orcid.org/0000-0002-9454-023X
Olga Perski
https://orcid.org/0000-0003-3285-3174
Kathleen Gali
https://orcid.org/0000-0002-6994-1146
Jamie Brown
https://orcid.org/0000-0002-2797-5428
Sabrina Kastaun
https://orcid.org/0000-0002-5590-1135

Prof. Dr. Daniel Kotz
Institute of General Practice (ifam)
Addiction Research and Clinical Epidemiology Unit
Centre for Health and Society (chs)
Medical Faculty and University Hospital Duesseldorf
Heinrich Heine University Duesseldorf
P.O. Box 101007
40001 Duesseldorf
Germany

Daniel.Kotz@med.uni-duesseldorf.de