SUCHT

Associations between tobacco smoking and self-reported SARS-CoV-2 / COVID-19 in the German population

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Abstract:	Aim: to assess the association between tobacco smoking status and self-reported SARS-CoV-2 infection, COVID-19 symptom severity, and symptom duration. 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. 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. In the general German population smokers appear to be as likely to acquire a corona infection as long-term ex- and never smokers.

Associations between tobacco smoking and self-reported SARS-CoV-2 / COVID-19 infections, disease severity, and duration in the German population

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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.

Key words

COVID-19; SARS-CoV-2; tobacco smoking; disease severity; disease duration; vaccination; population survey

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.

DEUTSCHE 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 Ergebnissen (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 Koronasymptome (aOR=0,84, 95%KI=0,59-1,20

bzw. aOR=0,88, 95%KI=0,55-1,38) und Dauer der Koronasymptome (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.

Diskussion

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)

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, Yang, Xu, Xu, & Liu, 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, Fuchs, Gardner, Lazartigues, & Yue, 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, Suddek, Filippidis, Majeed, & Coronini-Cronberg, 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.(David Simons, Lion Shahab, Jamie Brown, & Olga Perski; D. Simons, L. Shahab, J. Brown, & O. Perski, 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).(David 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, Li, He, Kwok, & Schooling, 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; D. 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 Supplementary Table 3a/b).

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 Supplementary Figure S1 for causal diagrams): years of age (continuous variable), 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 persosn 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%; Table1 and Table S1). 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 Supplementary Figure S2). Among the 872 people with an infection, 610 (70.0%) reported a low symptom severity (including n=148 without symptoms; Table1 and Table S2). 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 (Table1 and Table S3c).

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 (Tables S4-S6). 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 (Table S5). 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 (Table S6). 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: Tables S7). 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.

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,(Daniela 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., 2022; Toda et al., 2022; Tsatsakis et al., 2021; Uysal, Gümüş, Bektöre, Bozkurt, & Gözalan, 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.(David 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.(David 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, Hillman, Playford, & Hishmeh, 2021) Longitudinal population studies from the UK and the US reported prevalence rates for long COVID between 10-38%.(Whitaker et al., 2022; Wu, Ailshire, & Crimmins, 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.

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STATEMENTS AND DECLARATIONS

Statement of 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).

Declaration of Interest Statement

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.

Author Contributions Statement

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.

Data Availability Statement

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

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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)

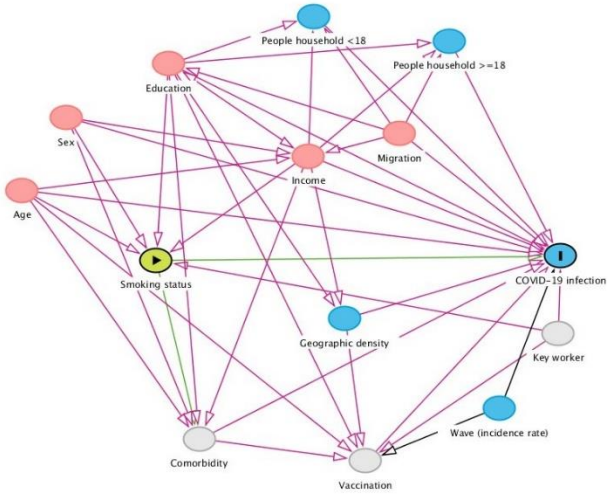
Data presented as column percentage (number), unless stated otherwise. †In people ever infected with SARS-CoV-2 (314 current smokers, 134 long-term ex-smokers, 420 never smokers, 4 missings). ‡In people with at least mild symptoms (250 current smokers, 107 long-term ex-smokers, 315 never smokers, 52 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

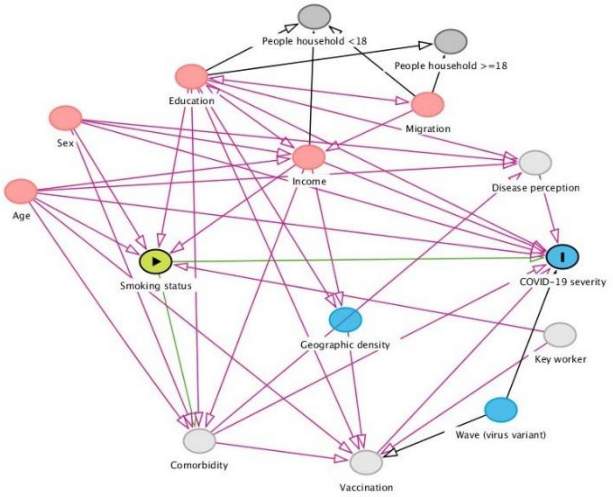
Smoking status	Infection yes vs. no infection aOR (95%CI) n=14,730	Symptom severity high vs. low aOR (95%CI) n=800	Symptom duration in months aβ (95%CI) n=626
Current	1.02 (0.86-1.20)	0.84 (0.59-1.20)	-0.09 (-0.45-0.28)
Long-term ex-smoking	1.03 (0.83-1.28)	0.88 (0.55-1.38)	0.002 (-0.48-0.48)
Never smoking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

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.

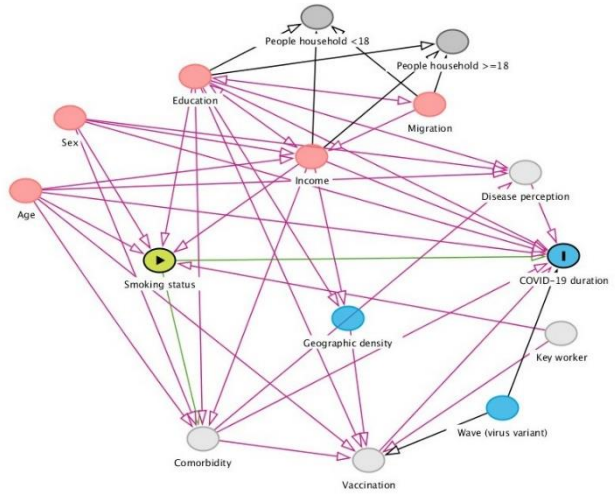
APPENDIX

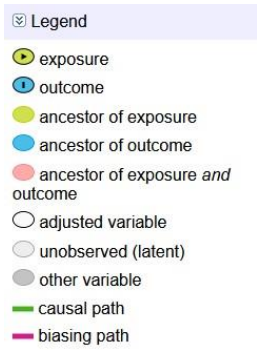


(a) outcome: infection



(b) outcome: severity





(c) outcome: duration

Figure S1a-c: Causal diagrams indicating the hypothetical associations between exposure, the outcomes – (a) corona infection, (b) symptom severity, (c) symptom duration – and potential confounding factors. The diagrams were drawn using the website http://dagitty.net.(Textor, van der Zander, Gilthorpe, Liśkiewicz, & Ellison, 2017)

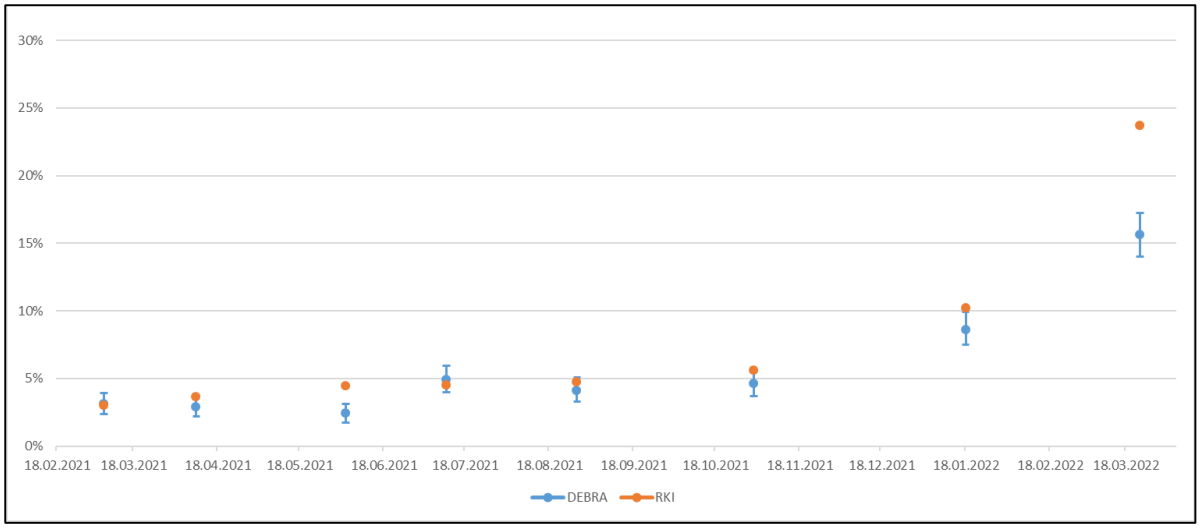


Figure S2: Weighted lifetime prevalence of corona infection rates at different time points of the DEBRA waves estimated with DEBRA data (blue dots, with 95%CIs) compared with official cumulative corona infection rates from the Robert Koch Institute (RKI, orange dots). The time points were defined as the days at which at least 50% of the DEBRA respondents had been interviewed during the time span of field work of the respective waves 28-35. The RKI rates were calculated by dividing the cumulative number of COVID-19 cases at the respective time point (as reported on http://corona.rki.de) by the total German population in the same year (as reported on https://www.destatis.de). The difference between the DEBRA estimated and the RKI figure at the time point of the last wave may partly be explained by the fact that the RKI figure includes people who have been infected more than one time. Such multiple infections have constantly increased since the start of the pandemic.

TABLE S1: Responses to the outcome corona infection in total sample (n=16,028)

"Have you ever been tested for the corona virus by healthcare personnel (no self-test)?"	**N (%)**
1. Yes, and I have tested positive at least once	872 (5.4)
2. Yes, but I have always tested negative	10,932 (68.2)
3. Yes, but I am still waiting for the result	30 (0.2)
4. No, I have never been tested for the corona virus	4,117 (25.7)
5. I don't know if I have ever been tested for the corona virus	77 (0.5)
6. No response	0

TABLE S2: Responses to the outcome corona symptom severity in subsample of people with a corona infection (n=872)

"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?"	**N (%)**
1. I had no symptoms or the test result was probably wrong	148 (17.0)
2. I only had mild symptoms	462 (53.0)
3. I had severe symptoms, but could cure myself at home	233 (26.7)
4. I had severe symptoms and had to get treatment in a hospital	19 (2.2)
5. In the hospital I needed intensive care treatment or had to be intubated	6 (0.7)
6. No response	4 (0.5)

Responses 1-2 indicating low symptom severity and 3-5 high symptom severity.

TABLE S3: Responses to the outcome corona symptom duration in subsample of people with a corona infection and symptoms of any degree (n=724)

a) "How long ago was your corona disease?"	**N (%)**
1. In the past month	74 (10.3)
2. 1-3 months	152 (21.1)
3. 3-6 months	177 (24.6)
4. 6-9 months	143 (19.9)
5. 9-12 months	116 (16.1)
6. Longer than 12 months	55 (7.6)
7. No response	3 (0.4)
b) "How long did the complaints of your corona disease last approximately?"	**N (%)**
1. Until today	74 (10.3)
2. 1 month	449 (62.4)
3. 1-3 months	107 (14.9)
4. 3-6 months	27 (3.8)
5. 6-9 months	9 (1.3)
6. 9-12 months	3 (0.4)
7. Longer than 12 months	3 (0.4)
8. No response	48 (6.7)
c) Metric scale of corona symptom duration based on responses to a) and b)†	**N (%)**
1. 0.5 months	66 (9.8)
2. 1 month	409 (60.9)
3. 1.5 months	120 (17.9)
4. 4.5 months	42 (6.3)
5. 7.5 months	20 (3.0)
6. 10.5 months	7 (1.0)
7. 12 months or longer	8 (1.2)
8. Missing	52 (7.2)

†N.B. The two variables a) and b) were combined into the following output parameters for symptom duration, resulting in a metric scale ranging from 0.5 to 12 months:

When did disease start?		**How long did complaints last?**							
		today	**1m**	**1-3m**	**3-6m**	**6-9m**	**9-12m**	**>12m**	**n.r.**
	<1m	0.5m	0.5m	1m	1m	1m	1m	1m	n.r.
	1-3m	1.5m	1m	1.5m	3m	3m	3m	3m	n.r.
	3-6m	4.5m	1m	1.5m	4.5m	4.5m	4.5m	4.5m	n.r.
	6-9m	7.5m	1m	1.5m	4.5	7.5m	7.5m	7.5m	n.r.
	9-12m	10.5m	1m	1.5m	4.5	7.5m	10.5m	10.5m	n.r.
	>12m	12m	1m	1.5m	4.5	7.5m	10.5m	12m	n.r.
	n.r.	n.r.	1m	1.5m	4.5	7.5m	10.5m	12m	n.r.

M = month. N.r. = no response (missing). Output parameters marked red indicate invalid combinations which have been corrected (imputed).

TABLE S4: Sensitivity analyses (different outcome definitions†‡) of the associations between smoking status and corona infection and corona symptom severity, adjusted for potential confounders

Smoking status	Infection† yes vs. no infection aOR (95%CI) n=14,669	Symptom severity‡ high vs. low aOR (95%CI)
Current	1.02 (0.68-1.20)	0.37 (0.11-1.18)
Long-term ex-smoking	1.03 (0.83-1.28)	0.52 (0.14-1.96)
Never smoking (reference)	1	1

aOR = adjusted odds ratio. 95%CI = 95% confidence interval around OR. OR 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. †Responders "I don't know if I have ever been tested" excluded. ‡Symptom severity defined as low = no hospitalisation versus high = hospitalisation ("I had severe symptoms and had to get treatment in a hospital" or "In the hospital I needed intensive care treatment or had to be intubated.")

TABLE S5: 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

Smoking status	Infection yes vs. no infection aOR (95%CI) n=5,447	Symptom severity high vs. low aOR (95%CI) n=133	Symptom duration in months aβ (95%CI) n=90
Current	0.86 (0.57-1.28)	1.82 (0.72-4.62)	0.92 (-0.47-2.30)
Long-term ex-smoking	0.83 (0.51-1.37)	2.34 (0.78-7.04)	0.58 (-0.87-2.02)
Never smoking (reference)	1	1	1

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. The analyses were restricted to respondents to waves 28-30 (waves 31-35 excluded).

TABLE S6: Sensitivity analyses (restriction to waves 34-35 in which data on the vaccination status of the respondents were collected) of the 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=3,755	Symptom severity high vs. low aOR (95%CI) n=451	Symptom duration in months aβ (95%CI) n=377
Current	1.06 (0.84-1.33)	0.67 (0.41-1.07)	-0.09 (-0.46-0.29)
Long-term ex-smoking	1.10 (0.81-1.50)	0.92 (0.50-1.72)	-0.12 (-0.64-0.41)
Never smoking (reference)	1	1	1

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, SARS-CoV-2 vaccination, and wave of the survey. The analyses were restricted to respondents to waves 34-35 (waves 28-33 excluded).

TABLE S7: Post-hoc ancillary sensitivity analysis (including an interaction between smoking status and wave of the survey) of the associations between smoking status and corona infection, adjusted for potential confounders

Interaction term	Infection yes vs. no infection aOR (95%CI) n=14,730
Current smoking * wave	1.10 (1.01-1.19)
Long-term ex-smoking * wave	1.01 (0.91-1.13)
Never smoking * wave (reference)	1

aOR = adjusted odds ratio. 95%CI = 95% confidence interval around OR. OR adjusted for: age, sex, migration background, people in household 18+ years, people in household aged <18 years, income, education, and region of living. Wave of the survey was used on a metric scale for the interaction with smoking status.

Associations between tobacco smoking and self-reported SARS-CoV-2 / COVID-19 infections, disease severity, and duration in the German population

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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 ~~infection~~ (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.

Key words

COVID-19; SARS-CoV-2; tobacco smoking; disease severity; disease duration; vaccination; population survey

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.

DEUTSCHE 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 ~~deutschen~~ 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 Ergebnissen (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 Koronasymptome (aOR=0,84, 95%KI=0,59-1,20

bzw. aOR=0,88, 95%KI=0,55-1,38) und Dauer der Koronasymptome (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.

Diskussion

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 ~~illness~~disease caused by the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. (World Health Organization, 2021) Due to its high transmissibility, governments ~~around the world~~ 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 ~~August~~ October 3rd, 2023~~29th, 2022~~, there have been an estimated total of 3~~82~~ million cases and ~~147,104~~ 168,935 deaths due to COVID-19 in Germany.(John Hopkins University & Medicine) ~~At current, 76% for the population of Germany has been fully vaccinate with the result that severity of illness and therefore deaths have considerably dropped since its highest peak in January 2021 with over 800 daily deaths reported to below approximately 100 in August 2022.[4]~~

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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, Yang, Xu, Xu, & Liu, 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, Fuchs, Gardner, Lazartigues, & Yue, 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, Suddek, Filippidis, Majeed, & Coronini-Cronberg, 2020) Furthermore, behavioural factors might play a role such as risk-~~averting~~ reducing behaviour (e.g., ~~gathering socially~~ meeting other people rather outdoors than indoors~~more outside~~, 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.(David Simons, Lion Shahab, Jamie Brown, & Olga Perski; D. Simons, L. Shahab, J. Brown, & O. Perski, 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).(David 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, Li, He, Kwok, & Schooling, 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.~~(some of which not yet peer reviewed)~~ (Barchuk et al., 2021; Carrat et al., 2021; D. Gornyk et al., 2021; Merkely et al., 2020; Radon et al., 2021; Richard et al., 2022; Wagner et al., 2021)~~, did not primarily focus on the association between smoking and SARS-CoV-2 / COVID-19.~~ 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 ~~people~~ 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

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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).

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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 ~~people~~ 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 ~~illness~~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 ~~people~~ 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 ~~illness~~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 ~~illness~~disease last approximately?" Response options: (1) until today; (2) 1 month; (3) 1-3 months; (4) 6-9 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 Supplementary Table 3a/b).

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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 ~~and~~ due to their corona symptoms).

Potential confounding variables

We included the following potential confounding variables from the DEBRA database in our adjusted analyses (see Supplementary Figure S1 for causal diagrams): years of age (continuous variable), sex (binary: female, male), migration background (binary: ~~yes~~at least one of the parents born abroad, none), number of ~~people~~ persons in the household aged 18+ years, number of ~~people~~ persosn 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

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(January/February 2022; ~~)~~also here, we relied on self-report) and ~~are~~ 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.

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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%; Table1 and Table S1). 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 ~~very similar~~ comparable to the official infection rates from the Robert Koch Institute (see Supplementary Figure S2). Among the 872 people with an infection, 610 (70.0%) reported a low symptom severity (including n=148 without symptoms; Table1 and Table S2). 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 (Table1 and Table S3c).

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 (Tables S4-S6). 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 (Table S5). 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 (Table S6). 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: Tables S7). 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.

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,(Daniela 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., 2022; Toda et al., 2022; Tsatsakis et al., 2021; Uysal, Gümüş, Bektöre, Bozkurt, & Gözalan, 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.(David 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.(David 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, Hillman, Playford, & Hishmeh, 2021) Longitudinal population studies from the UK and the US reported prevalence rates for long COVID between 10-38%.(Whitaker et al., 2022; Wu, Ailshire, & Crimmins, 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 ~~people~~ persons who ~~cannot easily be identified as~~ may or may not be healthcare ~~personnel~~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 ~~people~~ participants ~~experiences~~ 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.

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STATEMENTS AND DECLARATIONS

Statement of 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).

Declaration of Interest Statement

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.

Author Contributions Statement

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.

Data Availability Statement

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

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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¥		89.21,282 (1,28289.2)	586 93.3 (58693.3)	93.9 1,848 (1,84893.9)

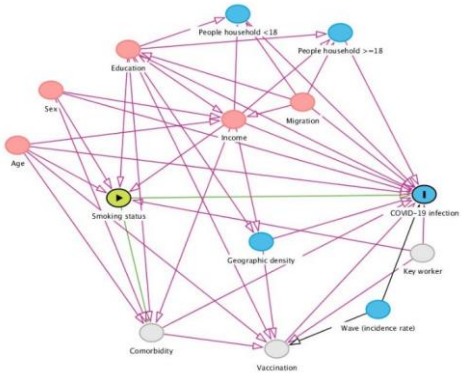
Data presented as column percentage (number), unless stated otherwise. †In people ever infected with SARS-CoV-2 (314 current smokers, 134 long-term ex-smokers, 420 never smokers, 4 missings). ‡In people with at least mild symptoms (250 current smokers, 107 long-term ex-smokers, 315 never smokers, 52 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

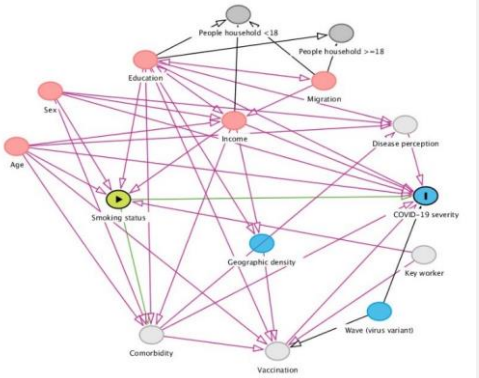
Smoking status	Infection yes vs. no infection aOR (95%CI) n=14,730	Symptom severity high vs. low aOR (95%CI) n=800	Symptom duration in months aβ (95%CI) n=626
Current	1.02 (0.86-1.20)	0.84 (0.59-1.20)	-0.09 (-0.45-0.28)
Long-term ex-smoking	1.03 (0.83-1.28)	0.88 (0.55-1.38)	0.002 (-0.48-0.48)
Never smoking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

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.

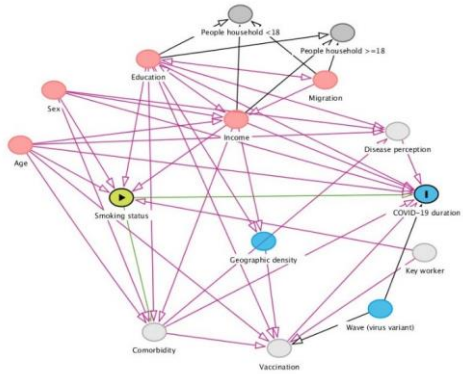
APPENDIX

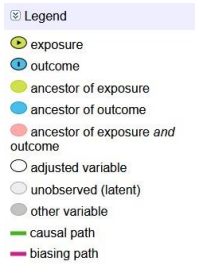


(a) outcome: infection



(b) outcome: severity





(c) outcome: duration

Figure S1a-c: Causal diagrams indicating the hypothetical associations between exposure, the outcomes – (a) corona infection, (b) symptom severity, (c) symptom duration – and potential confounding factors. The diagrams were drawn using the website http://dagitty.net.(Textor, van der Zander, Gilthorpe, Liśkiewicz, & Ellison, 2017)

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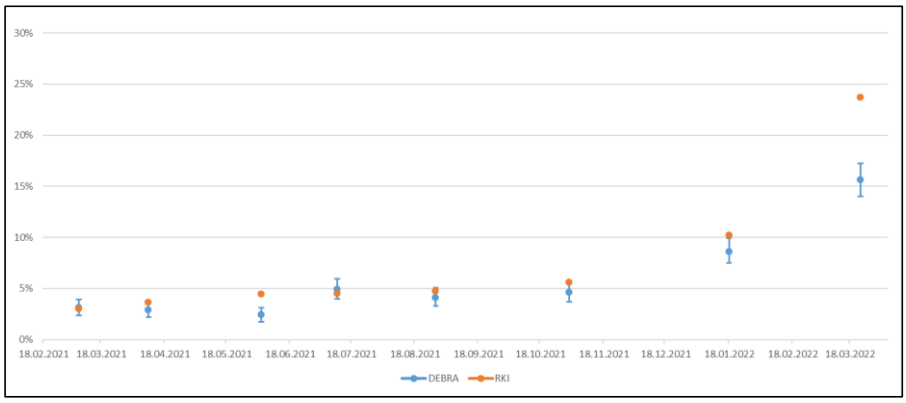

Figure S2: Weighted lifetime prevalence of corona infection rates at different time points of the DEBRA waves estimated with DEBRA data (blue dots, with 95%CIs) compared with official cumulative corona infection rates from the Robert Koch Institute (RKI, orange dots). The time points were defined as the days at which at least 50% of the DEBRA respondents had been interviewed during the time span of field work of the respective waves 28-35. The RKI rates were calculated by dividing the cumulative number of COVID-19 cases at the respective time point (as reported on http://corona.rki.de) by the total German population in the same year (as reported on https://www.destatis.de). The difference between the DEBRA estimated and the RKI figure at the time point of the last wave may partly be explained by the fact that the RKI figure includes people who have been infected more than one time. Such multiple infections have constantly increased since the start of the pandemic.

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TABLE S1: Responses to the outcome corona infection in total sample (n=16,028)

"Have you ever been tested for the corona virus by healthcare personnel (no self-test)?"	N (%)
1. Yes, and I have tested positive at least once	872 (5.4)
2. Yes, but I have always tested negative	10,932 (68.2)
3. Yes, but I am still waiting for the result	30 (0.2)
4. No, I have never been tested for the corona virus	4,117 (25.7)
5. I don't know if I have ever been tested for the corona virus	77 (0.5)
6. No response	0

TABLE S2: Responses to the outcome corona symptom severity in subsample of people with a corona infection (n=872)

"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 ~~illness~~disease?"	**N (%)**
1. I had no symptoms or the test result was probably wrong	148 (17.0)
2. I only had mild symptoms	462 (53.0)
3. I had severe symptoms, but could cure myself at home	233 (26.7)
4. I had severe symptoms and had to get treatment in a hospital	19 (2.2)
5. In the hospital I needed intensive care treatment or had to be intubated	6 (0.7)
6. No response	4 (0.5)

Responses 1-2 indicating low symptom severity and 3-5 high symptom severity.

TABLE S3: Responses to the outcome corona symptom duration in subsample of people with a corona infection and symptoms of any degree (n=724)

a) "How long ago was your corona ~~illness~~disease?"		**N (%)**
1.	In the past month	74 (10.3)
2.	1-3 months	152 (21.1)
3.	3-6 months	177 (24.6)
4.	6-9 months	143 (19.9)
5.	9-12 months	116 (16.1)
6.	Longer than 12 months	55 (7.6)
7.	No response	3 (0.4)
b) "How long did the complaints of your corona ~~illness~~disease last approximately?"		**N (%)**
1.	Until today	74 (10.3)
2.	1 month	449 (62.4)
3.	1-3 months	107 (14.9)
4.	3-6 months	27 (3.8)
5.	6-9 months	9 (1.3)
6.	9-12 months	3 (0.4)
7.	Longer than 12 months	3 (0.4)
8.	No response	48 (6.7)
c) Metric scale of corona symptom duration based on responses to a) and b)†		**N (%)**
1.	0.5 months	66 (9.8)
2.	1 month	409 (60.9)
3.	1.5 months	120 (17.9)
4.	4.5 months	42 (6.3)
5.	7.5 months	20 (3.0)
6.	10.5 months	7 (1.0)
7.	12 months or longer	8 (1.2)
8.	Missing	52 (7.2)

†N.B. The two variables a) and b) were combined into the following output parameters for symptom duration, resulting in a metric scale ranging from 0.5 to 12 months:

When did ~~illness~~disease start?	**How long did complaints last?**							
	today	**1m**	**1-3m**	**3-6m**	**6-9m**	**9-12m**	**>12m**	**n.r.**
<1m	0.5m	0.5m	1m	1m	1m	1m	1m	n.r.
1-3m	1.5m	1m	1.5m	3m	3m	3m	3m	n.r.
3-6m	4.5m	1m	1.5m	4.5m	4.5m	4.5m	4.5m	n.r.
6-9m	7.5m	1m	1.5m	4.5	7.5m	7.5m	7.5m	n.r.
9-12m	10.5m	1m	1.5m	4.5	7.5m	10.5m	10.5m	n.r.
>12m	12m	1m	1.5m	4.5	7.5m	10.5m	12m	n.r.
n.r.	n.r.	1m	1.5m	4.5	7.5m	10.5m	12m	n.r.

M = month. N.r. = no response (missing). Output parameters marked red indicate invalid combinations which have been corrected (imputed).

TABLE S4: Sensitivity analyses (different outcome definitions†‡) of the associations between smoking status and corona infection and corona symptom severity, adjusted for potential confounders

Smoking status	Infection† yes vs. no infection aOR (95%CI) n=14,669	Symptom severity‡ high vs. low aOR (95%CI)
Current	1.02 (0.68-1.20)	0.37 (0.11-1.18)
Long-term ex-smoking	1.03 (0.83-1.28)	0.52 (0.14-1.96)
Never smoking (reference)	1	1

aOR = adjusted odds ratio. 95%CI = 95% confidence interval around OR. OR 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. †Responders "I don't know if I have ever been tested" excluded. ‡Symptom severity defined as low = no hospitalisation versus high = hospitalisation ("I had severe symptoms and had to get treatment in a hospital" or "In the hospital I needed intensive care treatment or had to be intubated.")

TABLE S5: 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

Smoking status	Infection yes vs. no infection aOR (95%CI) n=5,447	Symptom severity high vs. low aOR (95%CI) n=133	Symptom duration in months aβ (95%CI) n=90
Current	0.86 (0.57-1.28)	1.82 (0.72-4.62)	0.92 (-0.47-2.30)
Long-term ex-smoking	0.83 (0.51-1.37)	2.34 (0.78-7.04)	0.58 (-0.87-2.02)
Never smoking (reference)	1	1	1

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. The analyses were restricted to respondents to waves 28-30 (waves 31-35 excluded).

TABLE S6: Sensitivity analyses (restriction to waves 34-35 in which data on the vaccination status of the respondents were collected) of the 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=3,755	Symptom severity high vs. low aOR (95%CI) n=451	Symptom duration in months aβ (95%CI) n=377
Current	1.06 (0.84-1.33)	0.67 (0.41-1.07)	-0.09 (-0.46-0.29)
Long-term ex-smoking	1.10 (0.81-1.50)	0.92 (0.50-1.72)	-0.12 (-0.64-0.41)
Never smoking (reference)	1	1	1

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, SARS-CoV-2 vaccination, and wave of the survey. The analyses were restricted to respondents to waves 34-35 (waves 28-33 excluded).

TABLE S7: Post-hoc ancillary sensitivity analysis (including an interaction between smoking status and wave of the survey) of the associations between smoking status and corona infection, adjusted for potential confounders

Interaction term	Infection yes vs. no infection aOR (95%CI) n=14,730
Current smoking * wave	1.10 (1.01-1.19)
Long-term ex-smoking * wave	1.01 (0.91-1.13)
Never smoking * wave (reference)	1

aOR = adjusted odds ratio. 95%CI = 95% confidence interval around OR. OR adjusted for: age, sex, migration background, people in household 18+ years, people in household aged <18 years, income, education, and region of living. Wave of the survey was used on a metric scale for the interaction with smoking status.

Ref.: Ms. No. SUCHT-D-23-00025
Associations between tobacco smoking and SARS-CoV-2 / COVID-19 infections, disease severity, and duration in the German population

Reviewers' comments:

Gutachter #1:
The presented manuscript presents a regression-based analysis using several assessment waves of a representative German population sample. Results show that the the hypotheses of current smokers being more or less likely to a) conceive a COVID-19 infection, to b) experience higher/lower symptom severity, and to c) experience longer/shorter symptom duration could be dismissd in this sample. The authors present a balanced discussin of these findings in the light of other current studies and present hypothetical explanations on differences as induced by selection biases, operationalization differences, and unaccounted confonders (such as vaccination status over time). I applaude them for their exemplary use of Open Access study protocol and a-priori analysis plan publication via https://osf.io/pzrv3. Given that major limitations are transparently presented and that the methodology is still suitable to present meaningful results, I have only minor revisions to propose to the
authors.

MINOR REVISIONS
1. Please consider to add the following limitation: The use of e-cigarettes or vaporizers has not been assessed although lung functioning may be influenced by repeated use of these devices.
AUTHOR RESPONSE: We would like to thank the reviewer for the positive feedback and useful suggestions. We have added the exclusion of e-cigarette use as a limitation.
CHANGES TO THE MANUSCRIPT: Discussion, limitations and strengths: “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.”

2. Please consider the following changes in wording:
AUTHOR RESPONSE: Thank you, we have incorporated these suggestions.

2.1. Running head: "COVID-19" instead of "corona"
CHANGES TO THE MANUSCRIPT: This has been changed as suggested.

2.2. Abstract: "corona infection status" instead of "corona infection"
CHANGES TO THE MANUSCRIPT: Abstract, methods: “Associations between smoking status (current, long-term ex-, never) and three self-reported outcomes (corona infection status, symptom severity, and symptom duration […]”

Similarly in the German Zusammenfassung. Methodik: “Die Zusammenhänge zwischen dem Rauchstatus (aktuelle*r Raucher*in, langjährige*r Ex-Raucher*in und Nie-Raucher*in) und drei selbstberichteten Ergebnissen (Corona-Infektionsstatus, Schweregrad der Corona-Symptome […]”

2.3. Background etc.: is "illness" the appropriate term for COVID-19 rather than "disease"?
CHANGES TO THE MANUSCRIPT: We have replaced “illness” with “disease” throughout the manuscript.

2.4. Background: "worldwide" instead of "around the world"
CHANGES TO THE MANUSCRIPT: This has been changed as suggested.

2.5. Background: "currently" instead of "At current"
CHANGES TO THE MANUSCRIPT: This has been changed as suggested.

2.6. Background: What is meant by "gathering socially more outside"?
CHANGES TO THE MANUSCRIPT: Background, third paragraph: “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) […]”

2.7. Methods: "2000 persons" instead of "2000 people". Furthermore, please note that numbers above 1,000 are frequently presented here using a comma, but not in this instance.
CHANGES TO THE MANUSCRIPT: Methods, first paragraph: “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.”

2.8. Methods: "subgroup of persons" or "participants" instead of "subgroup of people". The same applies to "number of people in the household"
CHANGES TO THE MANUSCRIPT: This has been changed as suggested.

2.9. Methods: consider to leave out "and" in "smokers stop smoking and due to their corona symptoms"
CHANGES TO THE MANUSCRIPT: This has been changed as suggested.

2.10. Results: "comparable" instead of "very similar"
CHANGES TO THE MANUSCRIPT: This has been changed as suggested.

2.11. Limitations: "persons who may or may not be healthcare professionals" instead of "people who cannot easily be identified as healthcare personnel"
CHANGES TO THE MANUSCRIPT: Discussion, limitation and strengths: “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.”

2.12. Conclusion: "The majority of PARTICIPANTS experienced mild symptoms and symptoms that last less than three months." instead of "The majority of people experiences mild symptoms and symptoms that last less than three months.". I find it important not to generalize on the total population as this would severely underestimate the detrimental health effects given that hospitalized cases are very likely underrepresented - not to mention deceased patients.
CHANGES TO THE MANUSCRIPT: Discussion, conclusion and recommendations: “The majority of participants experienced mild symptoms and symptoms that last less than three months.”

3. Please consider to provide additional details or explanations concerning the following points:
3.1. Title/Abstract: Due to the obvious limitations of self-report data, it might be considered to add "self-reported" to the title as well as to the research question in the abstract.
CHANGES TO THE MANUSCRIPT: Title: “Associations between tobacco smoking and self-reported SARS-CoV-2 / COVID-19 infections, disease severity, and duration in the German population.”
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.”

Similarly in the German Zusammenfassung. Einführung: “Unser Ziel war es, 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.”

3.2. Abstract: time frame regarding smoking status as well as COVID-19 outcomes, vaccinations status regarding which disease
CHANGES TO THE MANUSCRIPT: Abstract, results: “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 […]”

Similarly in the German Zusammenfassung. Ergebnisse: „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 […]“

3.3. Background: replace COVID-19 case numbers and vaccination estimations from August 222 with present ones as available through the cited source at: https://coronavirus.jhu.edu/region/germany .
CHANGES TO THE MANUSCRIPT: We have updated the case numbers in the former second paragraph of the Introduction and merged with the first paragraph: “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.”

The same is true for papers which were, at least in August 2022, "not yet peer reviewed" but are published now in 2023: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8888869/ and https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-021-06589-4
CHANGES TO THE MANUSCRIPT: We now cite the publications of these two papers: Radon, K., et al., From first to second wave: follow-up of the prospective COVID-19 cohort (KoCo19) in Munich (Germany). BMC Infectious Diseases, 2021. 21(1): p. 925; Gornyk, D., et al., SARS-CoV-2 Seroprevalence in Germany. Dtsch Arztebl Int, 2021. 118(48): p. 824-831. We subsequently revised the last but one paragraph of the Background: “The few high quality population studies did not primarily focus on the association between smoking and SARS-CoV-2 / COVID-19.”

3.4. Methods: Please add details on whether participants were reimbursed for participation.
CHANGES TO THE MANUSCRIPT: Methods, first paragraph: “Respondents were not reimbursed for participation.”

3.5. Methods: Does "migration background" apply to the person itself (as in "I have migrated to Germany in the past") or does it include persons born in German but with at least one parent who itself migrated to Germany?
CHANGES TO THE MANUSCRIPT: Methods, potential confounding variable: “We included the following potential confounding variables […]: migration background (binary: at least one of the parents born abroad, none) […]”

3.6. Methods: The paragraph on the vaccination variable is better suited in the limitations section.
CHANGES TO THE MANUSCRIPT: None – we prefer to keep this paragraph in the Methods section.

3.7. Methods: Please add information on the statistical software/version/packages that have been used.
CHANGES TO THE MANUSCRIPT: Methods, statistical analyses: “We used IBM® SPSS Statistics Version 27 for the analyses.”

3.8. Results: I was wondering if results for unadjusted models (i.e., only outcome by main predictor) would be informative to readers in order to understand the extent to which control variables explain variance. Furthermore, future analysis might use regression models that can account for certain missing types (i.e., completely missing at random/missing at random), e.g., https://cran.r-project.org/web/packages/finalfit/vignettes/missing.html. Especially in the second regression model with N=800 this would increase the sample size considerably (+72 / 8.2%).

CHANGES TO THE MANUSCRIPT: None – we carefully thought about our analyses and adjustments for potential confounders, and the exploration of variance in relation to these variables was not part of our a priori study protocol (https://osf.io/pzrv3). Thank you for the suggestion for future analyses.

3.9. Results/Table 1: In the line with vaccination status, the N is presented first and the percentage follows in parentheses, while all other lines present results in inverse order: % (N).
CHANGES TO THE MANUSCRIPT: Well spotted! We have changed this accordingly in Table 1.

3.10. Results: I would recommend to drop the "adjusted" in "adjusted Odds Ratio" if it refers to the inclusion of confounding variables in the regression model - Otherwise, if there were any additional statistical adjustment step / normalization step undertaken, then this should be clarified in the statistical analysis.
CHANGES TO THE MANUSCRIPT: None – the "adjusted Odds Ratio" indeed refers to the fact that models were adjusted for the potentially confounding factors, as stated under Methods, statistical analyses. We hope this is clear for the readers.

3.11. Results, post-hoc: I was wondering if the results in Table S7 (i.e., current smokers with highest risk increase over time) could be attributed to a lower rate of vaccinations in this very group.
CHANGES TO THE MANUSCRIPT: Good point. We have added the following sentence to the second paragraph of the Discussion: "Furthermore, the pronounced increase in infection rate in current smokers may be due to a lower vaccination rate in this very group."

4. Please revise the reference list as well as in-text citations carefully according to the journal's citation style.
CHANGES TO THE MANUSCRIPT: We have revised the citations and the reference list accordingly.

Gutachter #2:
Dear authors,
I would like to thank you for your work on the effects of smoking on SARS-CoV-2 infections. Your research provides valuable insights into a topic that is surrounded by contradictory statements. However, given the current situation where SARS-CoV-2 is not prominently discussed, it might be beneficial to briefly explain in the introduction why this article is still highly relevant.
AUTHOR RESPONSE: It is true that corona is less prominent in the news compared with previous years. However, particularly at the moment (winter season) cases are rising again, which will be associated with long-term consequences and new deaths (https://coronavirus.jhu.edu/region/germany). More importantly, however, is the incomplete evidence regarding the role of tobacco smoking and/or nicotine plays in the susceptibility of COVID-19 infection, disease severity, and symptoms. Our study aimed to add to the existing evidence. Such evidence is potentially useful for future efforts of prevention and risk communication.
CHANGES TO THE MANUSCRIPT: We have added the following sentence at the end of the Background section: "Evidence about the role of tobacco smoking and/or nicotine is potentially useful for future efforts of disease prevention and risk communication."

Regarding the formal presentation of your results, I suggest using interval notation for numerical values (e.g. odds ratios, confidence intervals) to increase clarity.
AUTHOR RESPONSE: We do not fully understand this comment – could you explain in more detail?
CHANGES TO THE MANUSCRIPT: None.

In the introduction, formulate the topic clearly and concisely. However, the references to the latest data on deaths and disease progression after vaccination only go up to 22 August. I recommend verifying and updating this information with more recent data, if available.
AUTHOR RESPONSE: Agree.

CHANGES TO THE MANUSCRIPT: In line with a comment from reviewer 1, we have updated the case numbers in the former second paragraph of the Introduction and merged with the first paragraph: "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."

In the Material and Methods section, it would be helpful to clarify the verification process of the tests performed by the medical staff. Was this verification based solely on the information provided by the respondent, or were the results at least supported by a written report from a laboratory or testing centre? Please explain this aspect in your manuscript.
AUTHOR RESPONSE: We relied on self-report.
CHANGES TO THE MANUSCRIPT: We have added the following sentence to the Methods, outcome: "We relied on self-report; the infection status was not verified by a written report from a laboratory or test station."

Was the vaccination status of the vaccinated persons mentioned in the interviews checked? If so, how was this check carried out? If not, it would be helpful to indicate in the manuscript that the immunisation status is based purely on the interview.
AUTHOR RESPONSE: Also here, we relied on self-report.
CHANGES TO THE MANUSCRIPT: We have revised the last paragraph under Methods, potential confounding variables: "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."

In the Discussion section, the non-significant trend in smokers during the first wave (28-30) is addressed, suggesting a lower infection rate compared to non-smokers. While the explanation for the negative seroconversion is understandable, the conclusions drawn are somewhat difficult to understand. It would be helpful to clarify how your statement is meant. My current understanding is that the lower infection rate among smokers in the first wave could be due to undetectable infections (false negatives). In addition, your results indicate a higher number of infected smokers compared to non-smokers. Is this increase due to a less effective vaccination response in smokers? If so, does this mean that the vaccine is less effective in smokers? I recommend clarification in your discussion regarding these interpretations of the results and better support of the argument with literature.
AUTHOR RESPONSE: Yes, various vaccination studies found that smokers had lower SARS-CoV-2 antibody titres compared with non-smokers. We have added a sentence to the second paragraph of the Discussion in the hope that this increases the clarity.
CHANGES TO THE MANUSCRIPT: Discussion, second paragraph: "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."

Thank you for your dedicated work on this study. Clarification and elaboration of the above points could, in my view, significantly improve the manuscript.
AUTHOR RESPONSE: We thank you for your thorough review and helpful suggestions.