Current smoking and SARS-CoV-2 infection: findings from the Italian cross-sectional EPICOVID19 internet-based survey.

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Current smoking and SARS-CoV-2 infection: findings from the Italian cross-sectional EPICOVID19 internet-based survey.

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Abstract

Background: Several studies reported a low prevalence of current smoking among hospitalized COVID-19 cases however, no definitive conclusions can be drawn.

Objective: We investigated the association of tobacco smoke exposure with the nasopharyngeal swab (NPS) test result for SARS-CoV-2 infection and the disease severity accounting for possible confounders.

Methods: The cross-sectional EPICOVID19 web-based survey was performed in an Italian population of 198,822 adults who filled in an online questionnaire between April 13 and June 2, 2020. For the present study we analyzed 6857 individuals with known NPS test result. The association of smoking status and the dose-response relationship with the positivity to NPS test and infection severity were analyzed using logistic and multinomial regression models adjusting for socio-demographic, clinical and behavioral characteristics.

Results: Out of the 6857 individuals, 63.2% had never smoked, 21.3% were former and 15.5% were current smokers. Compared to non-smokers, current smokers were younger, more educated, less affected by chronic diseases, reported less frequently COVID-like symptoms, were less hospitalized and tested for COVID-19. In multivariate analysis current smokers had almost halved odds of a positive NPS test (OR 0.54, 95% CI 0.45-0.65) compared to non-smokers. We also found a dose-dependent relationship with tobacco smoke: mild smokers (OR 0.76, 95% CI 0.55-1.05), moderate (OR 0.56, 95% CI 0.42-0.73) and heavy smokers (OR 0.38, 95% CI 0.27-0.53). This inverse association persisted also when considering the severity of the infection.

Conclusions: Current smoking was negatively associated with SARS-CoV-2 infection with a dose-dependent relation. Ad-hoc experimental studies are needed to elucidate the mechanisms underlying this association. Clinical Trial: ClinicalTrials.gov NCT04471701

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ABSTRACT

Background
Several studies reported a low prevalence of current smoking among hospitalized COVID-19 cases however, no definitive conclusions can be drawn.

Objective
We investigated the association of tobacco smoke exposure with the nasopharyngeal swab (NPS) test result for SARS-CoV-2 infection and the disease severity accounting for possible confounders.

Methods
The nationwide self-administered cross-sectional EPICOVID19 web-based survey was performed in an Italian population of 198,822 voluntary adults who filled in an online questionnaire between April 13 and June 2, 2020. For the present study, we analyzed 6857 individuals with known NPS test result. The associations of smoking status and the dose-response relationship with the positivity to NPS test and infection severity were calculated as odds ratios with 95% Confidence Intervals (OR, 95%CI) by means of logistic and multinomial regression models adjusting for socio-demographic, clinical, and behavioral characteristics.

Results
Out of the 6857 individuals (mean age 47.9 years, 65.9% females), 63.2% had never smoked, 21.3% were former and 15.5% were current smokers. Compared to non-smokers, current smokers were younger, more educated, less affected by chronic diseases, reported less frequently COVID-like symptoms, were less hospitalized and tested for COVID-19. In
multivariate analysis current smokers had almost halved odds of a positive NPS test (OR 0.54, 95% CI 0.45-0.65) compared to non-smokers. We also found a dose-dependent relationship with tobacco smoke: mild smokers (OR 0.76, 95% CI 0.55-1.05), moderate (OR 0.56, 95% CI 0.42-0.73) and heavy smokers (OR 0.38, 95% CI 0.27-0.53). This inverse association persisted also when considering the severity of the infection. Current smokers had a statistically significant lower probability of having asymptomatic (OR 0.50 95%CI 0.27-0.92), mild (OR 0.65 95%CI 0.53-0.81), and severe infection (OR 0.27 95%CI 0.17-0.42) compared to never smokers.

**Conclusions**

Current smoking was negatively associated with SARS-CoV-2 infection with a dose-dependent relation. Ad-hoc experimental studies are needed to elucidate the mechanisms underlying this association.

**Trial Registration:** ClinicalTrials.gov NCT04471701

**Keywords**

SARS-CoV-2; COVID-19; smoking habit; dose-response relationship; nasopharyngeal swab testing; infection severity; web-based survey; self-reported; cross-sectional design.
INTRODUCTION

In June 2020 the WHO released a report warning that smoking habits could be associated with adverse coronavirus disease (COVID-19) prognosis. Based on extensive evidence, the report highlighted the negative impact of tobacco use on lung health and its causal association with both viral and bacterial respiratory infections. In humans, the spike protein (S-protein) – Angiotensin-converting enzyme 2 (ACE2) binding pathway constitutes a cell-binding site for the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) S-protein. ACE2 was found upregulated in the small airway epithelia of smokers, which partially explain the increased risk of severe COVID-19 in this sub-population.

However, studies from several European and non-European countries including China, USA, Mexico, Israel, France, UK, and Italy have shown an unusual low proportion of active smokers among hospitalized patients with respect to the general population. Moreover, a negative association between current smoking prevalence and COVID-19 occurrence at the population level was found in an ecological study performed in 38 European countries and in a few non-hospitalized populations. Possible biological mechanisms have been proposed to explain the counterintuitive underrepresentation of smokers among COVID-19 patients strengthening the concept of “smoker’s paradox”.

Nevertheless, possible explanations for these findings could be due to biases in the available data. In fact, considering the emergency of the epidemic, it has been suggested...
that the smoking status and smoking history (included the duration, the quantity or the time from possible smoking cessation) of patients could have not been accurately recorded or some patients were unable to report their smoking habits, leading to a misclassification of smoking status. Moreover, the ascertainment of smoking exposure has not been supported by the use of objective biomarkers [19-20], or again, smokers may be taking medications or having behaviors, inducing some protection against COVID-19 [CITATION Leu \ 1040 ].

Finally, the majority of the studies conducted to date, were performed in clinical settings without a detailed evaluation of possible confounders (comorbidities, area of residence socio-economic factors) and, in meta-analyses, heterogeneous studies were pooled together [CITATION Gru \ 1040 ].

Bearing these considerations in mind, in the present study we postulated that smoking habit was associated with both SARS-CoV-2 infection and disease severity in a general population, with a dose-response relationship independently from confounding factors not considered in previous studies. To verify this hypothesis, we used data from the self-administered EPICOVID19 web-based survey with the aims: 1) to evaluate the frequency distribution of socio-demographic, clinical and behavioural characteristics among participants according to smoking status; and 2) to investigate the cross-sectional association of smoking patterns (intensity and duration) with SARS-CoV-2 nasopharyngeal swab (NPS) test result and infection severity, taking into account for a wide number of potential confounding factors.

**METHODS**

**Study design, setting and population**

The study population was derived from the EPICOVID19 national internet-based survey [24] conducted using a cross-sectional research design in a self-selected sample of adult volunteers living in Italy during the lockdown in March-May 2020 (during this same period
the total confirmed COVID-19 infected cases in Italy were 233,515 [25]). The study procedures were described elsewhere [24]. Briefly, the link to the web-based survey was implemented using the EUSurvey management tool, uploaded, and shared from April 13 to June 2, 2020 via several channels: e-mails, social media platforms (Facebook, Twitter, Instagram, Whatsapp), press releases, internet pages, local radio and TV stations, institutional websites, mailing lists, and the study website. The inclusion criteria to take part in the survey were age ≥18 years; access to a mobile phone, computer, or tablet with internet connectivity; and provision of online consent to participate in the study. Out of the 198,822 participants who provided the consent to participate and completed the on-line survey, 254 had missing data about smoking duration, 191,250 did not perform the NPS test, and 461 did not yet know the NPS test result leading to a final sample of 6,857 (3.4%) participants for the present analysis (Figure 1).

Compared to people excluded (N=191,250) for not having performed the NPS test, those included (N=6857) in the analysis were more likely to be females, less educated, more employed, white collars, healthcare professionals, residents in Northern regions, more affected by chronic diseases, more frequently vaccinated for flu and pneumococcal, more likely to report symptoms, more frequently hospitalized, never smokers, living in big suburbs/cities and crowded houses, more frequently reported contact with COVID-19 cases and called the emergency numbers, and had a lower self-perceived health status (Supplementary Table 1).

The Ethics Committee of the Istituto Nazionale per le Malattie Infettive I.R.C.C.S. Lazzaro Spallanzani (Protocol No. 70, 12/4/2020) approved the EPICOVID19 study protocol. When participants first accessed the web-based platform, they were informed about the study and filled in the informed consent form. Participation was voluntary and no compensation was expected for respondents. Data were handled and stored in accordance with the European
Union General Data Protection Regulation (EU GDPR) 2016/679, and data transfer was safeguarded by encrypting/decrypting and password protection. The study was registered (ClinicalTrials.gov NCT04471701).

Data Collection and variables definition

The EPICovid19 study was established as a collaborative project of a working group including epidemiologists, physicians expert in infectious diseases, biostatisticians, and public health professionals with the aim to improve SARS-CoV-2-related knowledge. To guarantee the maximal comparability with other studies, several questions were defined based on standardized and validated questionnaires, as elsewhere described in details[ CITATION Sel \l 1040 ][ CITATION EPI \l 1040 ][ CITATION Noa \l 1040 ]. The participants were asked to complete an anonymous 38-item questionnaire (Annex 1), which mainly contained mandatory and closed questions divided into six sections: socio-demographic, clinical features, personal characteristics, behaviours before the lockdown, lifestyles, and behaviours following the lockdown (Supplementary file).

Smoke exposure

A number of questions on present and past smoking habit were asked in the questionnaire. These included smoking status defined as never smoked (persons who had never smoked regularly or had smoked less than 100 cigarettes), former smokers (regular smokers who have smoked at least 100 cigarettes during the lifetime and did not smoke at the time of the survey), and current smokers [ CITATION htt6 \l 1040 ]. In order to explore the dose-response effect, we created a variable by collapsing data on smoking status and number of years of smoke as follows: former smokers (categorized for smoking duration $\leq$ 10 years or $> 10$ years) and current smokers grouped in mild smoker ($<$10 cigarettes/day for $<15$ years), moderate smokers ($<$ 10 cigarettes/day for more than 15 years or $>10$ cigarettes/day for less than 15 years), and heavy smoker ($>10$ cigarettes/day for more than
Main outcomes

We investigated two different outcomes: 1) positive result to the NPS molecular test; and 2) SARS-CoV-2 infection severity by combining information on NPS test, symptoms and hospitalization for COVID-19 defined as follows:

- **No infection**: negative NPS test
- **Asymptomatic infection**: positive NPS test without symptoms
- **Mild infection**: positive NPS test with at least one symptom
- **Severe infection**: positive NPS test and pneumonia or hospitalization for COVID-19.

Statistical analysis

The continuous variables were represented as mean and standard deviation (SD) and the categorical variables as counts and percentages. Continuous and categorical data according to smoking status were compared using one-way analysis of variance (ANOVA) and chi-square test respectively. To explore the association between smoking habit and positive versus negative NPS test results and 4-level infection severity dependent variable (no infection, asymptomatic infection, mild infection, and severe infection), logistic-regression and multinomial-regression models were used to estimate the odds ratios (ORs) and 95% Confidence Intervals (CIs). A first model (model 1) was only adjusted for age and sex. In the fully adjusted model (model 2) we further controlled for variables considered potential confounders as education, occupation, area of residence, heart diseases, lung diseases, hypertension, metabolic diseases, contact with suspected/confirmed COVID-19 cases, living area, crowding index, and living with at risk co-habitants. Models were applied considering separately the smoking status and the dose-response relationship as exposures. We explored our data for potential effect modification by sex, age, and education by adding cross-product terms of these variables to the regression models. When
heterogeneity was present, stratum-specific estimates were evaluated. Three sensitivity analyses were performed in order to evaluate whether the effect of smoking on SARS-CoV-2 infection was primarily due to the current amount of cigarettes smoked and/or to the smoking history during lifespan. In the first sensitivity analysis, we categorized current smokers based on years of smoking classified as ≤15, 15-30, and >30 years. Second sensitivity analysis explored the association between the number of cigarettes smoked categorized as less than 10 cigarettes/day or more than 10 cigarettes/day and NPT test. Third sensitivity analysis repeated the analysis by calculating the pack-years of smoking. We assigned a median number of cigarettes/day to each current smoking category (5 for 'less than 10 cig/day'; 15 for '10 to 20 cig/day'; 25 for 'more than 20 cig/day'), then we multiplied the number of packs per day (1 pack=20 cigarettes) by the number of years the person had smoked, and finally we tertilized the variable. All statistical analyses were performed using Stata 15.0 version (StataCorp LP, College station, Texas, USA), and a two-sided P-value <.05 was considered statistically significant.

RESULTS

Characteristics of participants

The participants' characteristics according to smoking status are summarized in Table 1, 2 and 3. The mean age of the whole sample was 47.9±14.1 years, 65.9% were females and 70.5% had university or higher degree. Out of the 6857 individuals, 63.2% (N=4334) had never smoked, 21.3% (N=1463) were former and 15.5% (N=1060) were current smokers. The 24.7% (N=1691) had a positive NPS test, among them 9.2% (N=156) were asymptomatic, 62.0% (N=1049) had mild infection, and 28.7% (N=486) reported conditions compatible with a severe infection. Compared with those who never smoked, current smokers were younger, with higher educational level, more frequently working as employers, healthcare professionals, and were frequently residents in Central and Southern
regions (Table 1).
Table 1. Socio-demographic characteristics of study participants with known molecular test results by smoking status (N=6,857), Italy, from April 13 to June 2, 2020.

| SOCIO-DEMOGRAPHIC CHARACTERISTICS | Never smoked | Former smoker | Current smoker | \( P \) value (current vs never) | \( P \) value (overall) | All |
|-----------------------------------|-------------|--------------|----------------|-------------------------------|-------------------------|-----|
| Sex, female                       |             |              |                |                               |                         |     |
|                                   | 2,991       | 807          | 420            | .42                           | .01                     |     |
|                                   | 69.0        | 55.2         | 70.1           |                               |                         |     |
| Age, years (mean, SD)             |             |              |                |                               |                         |     |
|                                   | 47.7        | 50.5         | 45.0           | >.001                         | .01                     |     |
|                                   | 14.7        | 13.1         | 12.4           |                               |                         |     |
| European ethnicity                |             |              |                |                               |                         |     |
|                                   | 4,281       | 1,458        | 1,052          | .20                           | .01                     |     |
|                                   | 98.8        | 99.7         | 99.3           |                               |                         |     |
| Education                         |             |              |                |                               |                         |     |
| Illiterate or primary school      | 359         | 96           | 30             |                               |                         |     |
|                                   | 8.3         | 6.6          | 5.0            |                               |                         |     |
| Middle or high school             | 893         | 347          | 126            |                               |                         |     |
|                                   | 20.6        | 23.7         | 21.0           |                               |                         |     |
| University or post-graduate       | 3,082       | 1,020        | 443            |                               |                         |     |
|                                   | 71.1        | 69.7         | 74.0           |                               |                         |     |
| Employment status                 |             |              |                |                               |                         |     |
| Employed                          | 3,626       | 1,223        | 548            | <.001                         | .01                     |     |
|                                   | 83.7        | 83.6         | 91.5           |                               |                         |     |
| Student                           | 125         | 18           | 19             |                               |                         |     |
|                                   | 2.9         | 1.2          | 3.2            |                               |                         |     |
| Unemployed                        | 63          | 28           | 8              |                               |                         |     |
|                                   | 1.5         | 1.9          | 1.3            |                               |                         |     |
| Retired                           | 291         | 144          | 8              |                               |                         |     |
|                                   | 6.7         | 9.8          | 1.3            |                               |                         |     |
| Other                             | 229         | 50           | 16             |                               |                         |     |
|                                   | 5.3         | 3.4          | 2.7            |                               |                         |     |
| Occupational cluster*             |             |              |                | .07                           | <.001                   |     |
| White collar                      | 3,428       | 1,173        | 804            | 804                           | 75.9                    |     |
| Blue collar                       | 58          | 37           | 17             |                               |                         |     |
| Others                            | 848         | 253          | 239            |                               |                         |     |
|                                   | 19.6        | 17.3         | 22.6           |                               |                         |     |
| Health professionals              |             |              |                |                               |                         |     |
| Northern                          | 3,318       | 1,084        | 755            |                               |                         |     |
| Central                           | 686         | 231          | 204            |                               |                         |     |
| Southern                          | 320         | 144          | 98             |                               |                         |     |
| Other                             | 10          | 4            | 3              |                               |                         |     |
|                                   | 0.2         | 0.3          | 0.3            |                               |                         |     |
| Italian area of residence         |             |              |                |                               |                         |     |
| Northern                          | 3,318       | 1,084        | 755            |                               |                         |     |
| Central                           | 686         | 231          | 204            |                               |                         |     |
| Southern                          | 320         | 144          | 98             |                               |                         |     |
| Other                             | 10          | 4            | 3              |                               |                         |     |

*White collar including legislators, senior officials and managers, professionals, technicians, associate professionals, clerks and service workers and shop and market sales workers; blue collar including skilled agricultural and fishery workers and craft and related trades workers, plant and machine operators and assemblers and elementary occupations, others including armed forces and unspecified occupations.
Current smokers were less affected by heart diseases (CVD), hypertension, oncological
diseases (1.5% vs 3.2%), and allergies. They were less dependent in daily activities;
were less vaccinated for flu and for pneumococcal infections, assumed less frequently
thyroid drugs and supplements, and more frequently anti-inflammatory drugs. Smokers
reported less frequently COVID-19-like symptoms as fever olfactory and taste disorders,
shortness of breath, cough, and pneumonia; they were less hospitalized for COVID-19,
had less frequently a NPS positive test, and in case of infection, they were less likely to
be asymptomatic, mild or severe symptomatic (Table 2).
Table 2. Clinical features of study participants with known molecular test results by smoking status (N=6,857), Italy, from April 13 to June 2, 2020.

| CLINICAL FEATURES                        | Never smoked N=4,334 (63.2%) | Former smoker N=1,463 (21.3%) | Current smoker N=1,060 (15.5%) | P value (current vs never) | P value (overall) | All N=6,857 |
|------------------------------------------|-----------------------------|--------------------------------|--------------------------------|---------------------------|-------------------|-------------|
| SELF-REPORTED DISEASES                   |                             |                                |                                |                           |                   |             |
| Lung diseases                            | 340 7.8                     | 130 8.9                        | 77 7.3                         | .53                       | .20               | 547 8.0     |
| Heart disease                            | 196 4.5                     | 76 5.2                         | 26 2.5                         | .01                       | .00               | 298 4.4     |
| Hypertension and/or medications          | 723 16.7                    | 326 22.3                       | 143 13.5                       | .01                       | <.001             | 1,192 17.4 |
| Oncological diseases                     | 138 3.2                     | 67 4.6                         | 16 1.5                         | .01                       | .00               | 221 3.2     |
| Liver diseases                           | 39 0.9                      | 14 1.0                         | 6 0.6                          | .28                       | .52               | 59 0.9      |
| Renal diseases                           | 52 1.2                      | 14 1.0                         | 10 0.9                         | .48                       | .64               | 76 1.1      |
| Metabolic diseases and/or medications    | 238 5.5                     | 86 5.9                         | 47 4.4                         | .17                       | .27               | 371 5.4     |
| Depression/anxiety and/or medications    | 505 11.7                    | 167 11.4                       | 122 11.5                       | .90                       | .97               | 794 11.6    |
| Immune system diseases                   | 431 9.9                     | 146 10.0                       | 88 8.3                         | .10                       | .25               | 665 9.7     |
| Surgical procedures last year            | 168 3.9                     | 82 5.6                         | 38 3.6                         | .66                       | .01               | 288 4.2     |
| Transplants                              | 12 0.3                      | 6 0.4                          | 0 0                            | .09                       | .13               | 18 0.3      |
| Allergies                                | 786 18.1                    | 223 15.2                       | 163 15.4                       | .04                       | .01               | 1,172 17.1 |
| Dependency in daily activities            | 209 4.8                     | 15 1.0                         | 9 0.9                          | <.001                     | <.001             | 233 3.4     |
| Flu shot during last autumn              | 1,542 35.6                  | 489 33.4                       | 273 25.8                       | <.001                     | <.001             | 2,304 33.6 |
| Anti-pneumococcal in the last 12         | 219 5.1                     | 73 5.0                         | 37 3.5                         | .03                       | .10               | 329 4.8     |
| SELF-REPORTED MEDICATIONS                |                             |                                |                                |                           |                   |             |
| Aspirin                                  | 192 4.4                     | 131 9.0                        | 46 4.3                         | .10                       | <.001             | 369 5.4     |
| Cholesterol treatment drugs              | 252 5.8                     | 161 11.0                       | 69 6.5                         | .39                       | <.001             | 482 7.0     |
| Oncological drugs                        | 42 1.0                      | 23 1.6                         | 6 0.6                          | .21                       | .04               | 71 1.0      |
| Chorticosteroids                         | 95 2.2                      | 39 2.7                         | 24 2.3                         | .89                       | .58               | 158 2.3     |
| Thyroid drugs                            | 369 8.5                     | 131 9.0                        | 64 6.0                         | .01                       | .02               | 564 8.2     |
| Anti-inflammatory drugs                  | 222 5.1                     | 108 7.4                        | 101 9.5                        | .00                       | <.001             | 431 6.3     |
| Supplements/vitamins                     | 928 21.4                    | 304 20.8                       | 190 17.9                       | .01                       | .04               | 1,422 20.7 |
| SELF-REPORTED SYMPTOMS                   |                             |                                |                                |                           |                   |             |
| Fever                                    | 1,221 28.2                   | 491 33.6                       | 184 17.4                       | .00                       | <.001             | 1,896 27.7 |
| Headache                                 | 1,594 36.8                   | 570 39.0                       | 397 37.5                       | .68                       | 0.33              | 2,561 37.4 |
| Muscle/bone pain                         | 1,476 34.1                   | 563 38.5                       | 340 32.1                       | .22                       | <.001             | 2,379 34.7 |

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### Clinical Features

| Clinical Feature                  | Never smoked (N=4,334) | Former smoker (N=1,463) | Current smoker (N=1,060) | P value (current vs never) | P value (overall) | All (N=6,857) |
|----------------------------------|------------------------|-------------------------|--------------------------|---------------------------|------------------|---------------|
| Olfactory and taste disorders    | 903 (20.8%)            | 365 (25.0%)             | 180 (17.0%)              | .01                       | <.001            | 1,448 (21.1%) |
| Shortness of breath              | 643 (14.8%)            | 264 (18.1%)             | 127 (12.0%)              | .02                       | <.001            | 1,034 (15.1%) |
| Chest pain                       | 596 (13.8%)            | 224 (15.3%)             | 144 (13.6%)              | .89                       | .30              | 964 (14.1%)   |
| Heart palpitations               | 572 (13.2%)            | 185 (12.7%)             | 118 (11.1%)              | .07                       | .19              | 875 (12.8%)   |
| Gastrointestinal disturbances    | 1,210 (27.9%)          | 441 (30.1%)             | 275 (25.9%)              | .20                       | .06              | 1,926 (28.1%) |
| Conjunctivities                  | 527 (12.2%)            | 174 (11.9%)             | 117 (11.0%)              | .31                       | .60              | 818 (11.9%)   |
| Sore throat/rhinorrhea           | 1,579 (36.4%)          | 558 (38.1%)             | 392 (37.0%)              | .74                       | .50              | 2,529 (36.9%) |
| Cough                            | 1,537 (35.5%)          | 536 (36.6%)             | 294 (27.7%)              | <.001                     | <.001            | 2,367 (34.5%) |
| Pneumonia                        | 354 (8.2%)             | 170 (11.6%)             | 17 (3.0%)                | <.001                     | <.001            | 556 (8.1%)    |
| No symptoms                      | 1,154 (26.6%)          | 321 (21.9%)             | 308 (29.1%)              | .11                       | <.001            | 1,783 (26.0%) |
| Hospitalized for COVID-19        | 319 (7.4%)             | 175 (12.0%)             | 33 (3.1%)                | <.001                     | <.001            | 527 (7.7%)    |
| NPS test positive result         | 1,124 (25.9%)          | 407 (27.8%)             | 160 (15.1%)              | <.001                     | <.001            | 1,691 (24.7%) |

*Infection severity*

- No infection
- Asymptomatic
- Mild
- Severe

* No infection (negative NPS test), asymptomatic infection (positive NPS test without symptoms), mild infection (positive NPS test with at least one symptom), and severe infection (positive NPS test and pneumonia or hospitalizing for COVID-19).
They lived less frequently with co-habitants at risk, after the lockdown more frequently went out and used public transport, contacted less frequently the emergency number and were more afraid about the infection for themselves and for family members than no smokers (Table 3).
Table 3. Behavioural characteristics of study participants with known molecular test results by smoking status (N=6,857), Italy, from April 13 to June 2, 2020.

| BEHAVIOURAL CHARACTERISTICS                  | Never smoked N=4,334 (63.2%) | Former smoker N=1,463 (21.3%) | Current smoker N=1,060 (15.5%) | P value (current vs never) | P value (overall) | All N=6,857 |
|----------------------------------------------|-------------------------------|-------------------------------|-------------------------------|--------------------------|------------------|-------------|
| HOUSING CONDITIONS                           |                               |                               |                               |                          |                  |             |
| Traffic near house                           |                               |                               |                               |                          |                  |             |
| Low                                          | 1,880 43.4                    | 655 44.8                      | 461 43.5                      | .25                      | .17              | 2,996 43.7 |
| Moderate                                     | 1,499 34.6                    | 525 35.9                      | 388 36.6                      |                          |                  | 2,412 35.2 |
| High                                         | 955 22.0                      | 283 19.3                      | 211 19.9                      |                          |                  | 1,449 21.1 |
| Co-habitants at risk*                        | 934 21.6                      | 250 17.1                      | 182 17.2                      | .01                      | <.001            | 1,366 19.9 |
| Residence area                               |                               |                               |                               |                          |                  |             |
| Countryside                                  | 492 11.4                      | 164 11.2                      | 136 12.8                      |                          |                  | 792 11.6   |
| Small town                                   | 1,797 41.5                    | 609 41.6                      | 411 38.8                      |                          |                  | 2,817 41.1 |
| Suburbs > 100,000 inhabitants                | 772 17.8                      | 233 15.9                      | 198 18.7                      |                          |                  | 1,203 17.5 |
| City town > 100,000 inhabitants              | 1,273 29.4                    | 457 31.2                      | 315 29.7                      |                          |                  | 2,045 29.8 |
| Household crowding index#                    |                               |                               |                               | .33                      | .10              |             |
| Low                                          | 3,941 90.9                    | 1,354 92.6                    | 974 91.9                      |                          |                  | 6,269 91.4 |
| Middle                                       | 387 8.9                       | 105 7.2                       | 86 8.1                        |                          |                  | 578 8.4    |
| High                                         | 6 0.1                         | 4 0.3                         | 0 0                           |                          |                  | 10 0.2     |
| BEHAVIOURS BEFORE THE LOCKDOWN              |                               |                               |                               |                          |                  |             |
| Number of daily contacts                     |                               |                               |                               | .17                      | .01              |             |
| Less than 10                                 | 738 17.0                      | 293 20.0                      | 162 15.3                      |                          |                  | 1,193 17.4 |
| 10 or more                                   | 3,596 83.0                    | 1,170 80.0                    | 898 84.7                      |                          |                  | 5,664 82.6 |
| Physical activity                            |                               |                               |                               | .88                      | <.001            |             |
| > 2.5 h/week                                 | 1,099 25.4                    | 449 30.7                      | 275 25.9                      |                          |                  | 1,826 26.6 |
| 10 minutes to 2.5 h/week                     | 1,870 43.1                    | 631 43.1                      | 449 42.4                      |                          |                  | 2,950 43.0 |
| < 10 minutes/week                            | 1,363 31.5                    | 383 26.2                      | 336 31.7                      |                          |                  | 2,082 30.4 |

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### BEHAVIOURAL CHARACTERISTICS

| N (%) | Never smoked | Former smoker | Current smoker | \( P \) value (current vs never) | \( P \) value (overall) | All N
|-------|--------------|---------------|----------------|---------------------------------|------------------------|-------|
| 4,334 (63.2%) | 3,118 | 71.9 | 989 | 67.8 | 754 | 71.1 | .60 | .01 | 4,861 | 70.9 |
| 1,463 (21.3%) | 1,083 | 25.0 | 417 | 28.5 | 290 | 27.4 | 1.547 | 22.6 |
| 1,060 (15.5%) | 2,208 | 51.0 | 682 | 46.6 | 630 | 59.4 | 1,790 | 26.1 |

#### Weekly outing

| N (%) | Never | 1-3 times | 4 times or more | \( P \) value | \( P \) value | All N
|-------|--------|------------|----------------|--------------|--------------|-------|
| 6,857 | 1,043 | 24.1 | 18 | 12 | .249 | 24.9 |
| 1,083 | 1,083 | 25.0 | 417 | 28.5 | 290 | 27.4 | 1.790 | 26.1 |
| 2,208 | 2,208 | 51.0 | 682 | 46.6 | 630 | 59.4 | 3,520 | 51.3 |

#### Use of public transport

| N (%) | Never | 1-3 times a week | 4 times a week or more | \( P \) value | \( P \) value | All N
|-------|--------|------------------|-----------------------|--------------|--------------|-------|
| 6,857 | 4,186 | 96.6 | 1,423 | 97.3 | 1,008 | 95.1 | 6,617 | 96.5 |
| 1,043 | 1,083 | 25.0 | 417 | 28.5 | 290 | 27.4 | 1,050 | 15.5 |
| 2,208 | 2,068 | 51.0 | 682 | 46.6 | 630 | 59.4 | 3,520 | 51.3 |

### PERSONAL CHARACTERISTICS

#### Emergency number contact

| N (%) | No | No, but I went to a hospital on my own | Yes, and they did not suggest to me self-isolation | Yes, and they suggested to me self-isolation | Yes, I was sent to a hospital | \( P \) value | \( P \) value | All N
|-------|----------------|--------------------------------|--------------------------------|--------------------------------|----------------|--------------|--------------|-------|
| 3,721 | 2,323 | 53.6 | 722 | 49.4 | 676 | 63.8 | 3,721 | 54.3 |
| 168 | 103 | 2.4 | 47 | 3.2 | 18 | 1.7 | 168 | 2.5 |
| 395 | 235 | 5.4 | 88 | 6.0 | 72 | 6.8 | 395 | 5.8 |
| 2,048 | 1,361 | 31.4 | 448 | 30.6 | 239 | 22.6 | 2,048 | 29.9 |
| 525 | 312 | 7.2 | 158 | 10.8 | 55 | 5.2 | 525 | 7.7 |

#### Self-perceived health status

| N (%) | Good | Adequate | Bad | \( P \) value | \( P \) value | All N
|-------|-------|----------|-----|--------------|--------------|-------|
| 5,511 | 3,493 | 80.6 | 1,155 | 79.0 | 863 | 81.4 | 5,511 | 80.4 |
| 1,230 | 769 | 17.7 | 282 | 19.3 | 179 | 16.9 | 1,230 | 17.9 |
| 116 | 72 | 1.7 | 26 | 1.8 | 18 | 1.7 | 116 | 1.7 |

#### Afraid to be infected

| N (%) | Not | Neutral | Yes | \( P \) value | \( P \) value | All N
|-------|-----|--------|-----|--------------|--------------|-------|
| 2,478 | 1,556 | 35.9 | 521 | 35.6 | 401 | 37.8 | 2,478 | 36.1 |
| 1,355 | 918 | 21.2 | 253 | 17.3 | 184 | 17.4 | 1,355 | 19.8 |
| 3,024 | 1,860 | 42.9 | 689 | 47.1 | 475 | 44.8 | 3,024 | 44.1 |

#### Afraid for family members

| N (%) | Not | Neutral | Yes | \( P \) value | \( P \) value | All N
|-------|-----|--------|-----|--------------|--------------|-------|
| 1,099 | 669 | 15.4 | 251 | 17.2 | 179 | 16.9 | 1,099 | 16.0 |
| 696 | 514 | 11.9 | 118 | 8.1 | 64 | 6.0 | 696 | 10.2 |
| 5,062 | 3,151 | 72.7 | 1,094 | 74.8 | 817 | 77.1 | 5,062 | 73.8 |
In bold variables with a $P$-value <0.05.
*Elderly persons or anyone with immunocompromising or chronic disease conditions
#Number of co-habitants/number of rooms. §Suspected/confirmed
In comparison with never- and current smokers, former smokers were significantly older, retired, more affected by chronic conditions as heart diseases and hypertension, assumed more frequently aspirin, drugs for lowering cholesterol, oncological and thyroid drugs. They reported less frequently COVID-19 like symptoms and were more likely to be hospitalized for COVID-19.

**Association analyses**

In Supplementary table 2 and Figure 2 are shown the logistic regression results for positive NPS test. In the age- and sex-adjusted model, current smoking was significantly inversely associated with positive NPS test (OR 0.54 95%CI 0.45-0.65), with never smoker as reference category. Results did not change when potential confounders were accounted for in the fully adjusted model (aOR 0.54 95%CI 0.44-0.65). Being former smokers was not associated with positive NPS (aOR 1.03 95%CI 0.90-1.19) even when we considered the dose-response relationship, and the lifetime smoking duration (≤ 10 years and > 10 years). Adjusted odds ratio for testing positive was 0.76 in mild smokers (95%CI 0.55-1.05) although not statistically significant, 0.56 in moderate (95%CI 0.42-0.73), and 0.38 in heavy smokers (95%CI 0.27-0.53) suggesting a dose-response relation between smoking habit and NPS test.

Table 4 reports the association between smoking status and infection severity. Current smokers had a statistically significant lower probability of having asymptomatic (aOR 0.50 95%CI 0.27-0.92), mild (aOR 0.65 95%CI 0.53-0.81), and severe infection (aOR 0.27 95%CI 0.17-0.42) compared to never smokers. The inverse dose-dependent relationship persisted also when considering the gravity of the infection, showing a gradient of association across smoking patterns. Since we found a significant interaction between smoking status and age (P=0.001), we created a six-level indicator variable by combining age, dichotomized in ≤48 and >48 years (median), and smoking status. Compared to the never-smokers aged ≤ 48, never- or former smokers aged > 48 had
1.5 folds and 1.7 folds higher probability of a positive NPS test, respectively.
Table 4. Odds ratios* of SARS-CoV-2 severity° by smoking habit (N=6,857)

| Smoking habit          | No infection N=5,166 (75.3) | Asymptomatic infection N=156 (2.3) | Mild infection N=1,049 (15.3) | Severe infection N=486 (7.1) |
|------------------------|-----------------------------|-----------------------------------|-------------------------------|-------------------------------|
|                        | N (%)                       | OR (95% CI)                       | N (%)                        | OR (95% CI)                  | N (%)                       | OR (95% CI)                  |
| Never smoked           | 3210 (62.1)                 | 1 (ref.)                          | 117 (75.0)                   | 1 (ref.)                     | 697 (66.4)                  | 1 (ref.)                     |
| Former smokers        | 1056 (20.4)                 | 0.78                              | 27 (17.3)                    | 0.84-1.18                    | 225 (42.6)                  | 1.20                         | 0.97-1.50                    | 155 (31.9)                  |
| Current smokers       | 900 (17.4)                  | 0.50                              | 12 (7.7)                     | 0.53-0.81                    | 127 (66.4)                  | 0.27                         | 0.17-0.42                    | 21 (4.3)                    |
| Dose-response relationship |
| Never smoked           | 3210 (62.1)                 | 1 (ref.)                          | 117 (75.0)                   | 1 (ref.)                     | 697 (66.4)                  | 1 (ref.)                     | 310 (63.8)                  |
| Former smokers (≤ 10 yrs) | 487 (9.4)                  | 0.84                              | 9 (5.8)                      | 0.79-1.27                    | 99 (9.4)                    | 1.22                         | 0.88-1.69                    | 50 (10.3)                  |
| Former smokers (>10 yrs) | 569 (11.0)                 | 0.74                              | 18 (11.5)                    | 0.79-1.22                    | 126 (66.4)                  | 1.20                         | 0.92-1.55                    | 105 (21.6)                  |
| Mild smokers           | 249 (4.8)                   | 1.16                              | 4 (2.6)                      | 0.59-1.18                    | 42 (4.0)                    | 0.23                         | 0.07-0.73                    | 3 (0.6)                     |
| Moderate smokers      | 365 (7.1)                   | 0.42                              | 4 (2.6)                      | 0.49-0.91                    | 52 (5.0)                    | 0.35                         | 0.19-0.66                    | 11 (2.3)                    |
| Heavy smokers         | 286 (5.5)                   | 0.36                              | 4 (2.6)                      | 0.34-0.72                    | 33 (3.2)                    | 0.20                         | 0.09-0.43                    | 7 (1.4)                     |

*No infection (negative NPS test) – reference category, asymptomatic infection (positive NPS test without symptoms), mild infection (positive NPS test with at least one symptom), and severe infection (positive NPS test and pneumonia or hospitalizing for COVID-19).

*Adjusted for age, sex, education, occupation, area of residence, heart diseases, lung diseases, hypertension, metabolic and oncological diseases, contact with COVID-19 cases, living area, crowding index, and living with at risk co-habitants.

Mild smokers (<10 cigarettes/day and <15 yrs); Moderate smokers (<10 cigarettes/day for more than 15 years or >10 cigarettes/day for less than 15 years); Heavy smokers (>10 cigarettes/day for more than 5 yrs).

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The odds were reduced by 33% and 42% in current smokers aged ≤ 48 and > 48, respectively (Supplementary table 3). In sensitivity analyses, considering never smoker as reference category, we found that the inverse relationship between smoking and positive NPS test was stronger in heavy smokers (>10 cigarettes/day, aOR 0.42 95%CI 0.31-0.56), in long-term smokers (>30 years, aOR 0.40 95%CI 0.26-0.61), and in those in the highest pack-years categories (11.3-65, aOR 0.43 95%CI 0.32-0.58). In moderate smokers (≤10 cigarettes/day aOR 0.64 95%CI 0.51-0.81), more recent current smokers (≤ 15 years, aOR 0.70 95%CI 0.53-0.92, and among those in the lowest category of pack-years of smoking (0.5-4.9 aOR 0.73 95%CI 0.54-1.00), the odds reduction was lower (Figure 3, Supplementary table 4).

DISCUSSION

Principal findings

The present study evaluated the association between smoking habit and the odds for positive SARS-CoV-2 molecular test and infection severity in an Italian adult population recruited on-line during the first national lockdown. We found that current smoking was associated with a significant risk reduction of having a positive SARS-CoV-2 test and with a severe infection in a dose-response relationship even after taking into account for all the available confounding factors.

In our sample, the percentage of positive tests was 24.7% (1,691/6,857 participants), close to the positive test ratio shown by Romagnani and colleagues who reported for Italy, at the beginning of April 2020, an overall percentage of positive tests of 18.6%, with a marked regional difference ranging from 38.5% in Lombardy to 7.5% in Lazio[CITATION Rom 1040 ]. The relatively high percentage of positive tests reflects the initial phase of the pandemic spread, during which, in Italy, molecular tests were reserved to clinically relevant cases. This is in keeping with the low percentage of asymptomatic subjects in our sample: 2.3% of the overall evaluated sample and 9.2%...
among confirmed SARS-CoV-2 infection cases. Although the 70.5% of participants had a university or higher degree and the female gender was predominant (65.9%), the prevalence of smoking habits in our sample was quite similar to that known for the Italian general population. Indeed, we found that 63.2% of the included participants had never smoked, 21.3% were former smokers and 15.5% were current smokers. In Italy, the prevalence of former smokers is 23.0%, while active smokers represent the 18.4% of the population and those who never smoked are the 57.4% [CITATION IST \l 1040 ].

When compared to never smokers, current smokers had a lower prevalence of chronic conditions (50.8% vs 55.4%) including those known to be influenced by smoking habits, such as CVD and hypertension (2.5% vs 4.5% and 13.5% 16.7%, respectively). Former smokers were older and more frequently retired compared to never- and current smokers were and, as expected, more affected by chronic diseases as CVD and hypertension (5.2% and 22.3%, respectively). This finding is consistent with the successful smoking cessation obtained by subjects affected by hypertension and myocardial infarction [CITATION 40 \l 1040 ]. Current smokers had significantly fewer COVID-19-like symptoms and were less hospitalized for COVID-19 than never and former smokers and this is in agreement with a previous meta-analysis study showing a lower prevalence of current smokers among hospitalized COVID-19 patients [19].

We found that current smoking was associated with reduced odds of NPS positive by 46%. Analogously, Israel and colleagues [CITATION Smo \l 1040 ] found reduced odds by 53% for the association between current smoking and fatal or severe disease in a population-based study among over 3,000,000 adults in Israel. Similar results were observed in a study on middle-aged veterans in US in which smokers were less likely to test positive (OR 0.43) although there was no significant difference in hospitalization [CITATION Ren \l 1040 ]. A large cohort study of 17,278,392 adults from the general population in the UK found that current smoking was associated with
an increased risk of COVID-19-related death controlling for age and sex. However, after adjustment for multiple adjusted covariates (e.g. chronic respiratory diseases) the study found that smoking was associated with a risk lowered by 11% [32]. A negative association between smoking prevalence and COVID-19 occurrence at the population level was also found in an ecological study conducted in 38 European countries, although the authors cautioned that this association may not imply a causal relationship [CITATION Tsi \\ 1040 ].

In our study, we also observed a significant dose-response relationship between smoking habit and NPS test results. In the full-adjusted logistic model, mild smokers had 24% lower probability of positive NPS test, whereas moderate smokers and heavy smokers had, respectively, 44% and 62% lower probability with the respect to never smokers. Conversely, among former smokers we did not find a significant effect of the time interval (more or less than 10 years) since they quitted on the risk for SARS-CoV-2 infection. A French study evaluating the smoking habits among symptomatic COVID-19 inpatients and outpatients showed that, in both groups active smokers were less infected by COVID-19 when compared with the general population [33].

When we analysed the association between smoking habits and SARS-CoV-2 infection severity, we found that active smokers were less likely to develop severe infection. Furthermore, by evaluating NPS positive participants in relation to their reported infection severity, i.e., asymptomatic, mild, or severe infection, being a current smoker reduced the odds by 50%, 35% and 73%, respectively. Likewise, the dose-response effect found for positive NPS result, heavy smokers showed a lower risk of developing different levels of gravity of SARS-CoV-2 infection, in particular severe COVID-19 (80% odds reduction). The link between smoking and infection severity is highly controversial in literature. For example, in the previously cited meta-analysis, Farsalinos and colleagues reported that, although the risk for current smokers to be hospitalized was
lower than among non-smokers, current smokers were more likely to have an adverse outcome during the hospital admission [19]. In a population of over 2.4 million UK users of the Zoe COVID-19 Symptom Study app, Hopkinson found for current smokers a statistically significant OR of 1.14 of self-reporting a triad of three symptoms (fever, persistent cough, and shortness of breath) that, although to some extent attributable also to constipation or normal flu, the authors identified as suggestive of COVID-19. On the contrary, when analysing the stronger endpoint of positive SARS-CoV-2 test, they observed a lower smoking rate (7.4% among positive vs 9.3% among negative) leading to a reduced adjusted OR of 0.7 that they considered not generalizable to their general population, due to the physiological difference between tested and non-tested individuals [34]. In their systematic review, Vardavas and Nikitara concluded that smoking was associated with disease progression and increased adverse outcomes in COVID-19 positive patients [35], even though, in both meta-analyses, the authors acknowledged that their studies were conducted with limited availability of data, the included studies came mostly from hospital contexts, and their analyses were not adjusted for confounding factors. Similar methodological limitations have been reported in the meta-analysis conducted by Patanavanich who found smoking as a risk factor for progression of COVID-19 [36] conversely, Lippi and Henry did not observe any association [37].

Our findings, which highlight the existence of a negative association of current smoking with SARS-CoV-2 infection and its severity, drive the focus to possible suggestive explanations. Since ACE2 is necessary for infection of cells by SARS-CoV-2 [38], the risk of contracting a SARS-CoV-2 severe infection, as well as the risk of a disadvantageous clinical outcome, could be influenced by the number of available ACE2 receptors and by the receptor-ligand interaction of ACE2 and SARS-CoV-2 S protein [39]. As concerns the number of ACE2 receptors, nicotine would seem to have a
controversial role. Recent evidence indicates that a higher number of receptors are expressed in smoker's lung tissues [40]. On the other hand, it has been suggested that nicotine downregulates the expression and/or the activity of ACE2 [41]. However, a better disease outcome was associated to an overexpression of ACE2, able to compensate the negative effects of the ACE2 downregulation induced by the cell entry of SARS-CoV-2 [42]. Moreover, a direct role of nicotine on disrupting spike protein glycosylation, could in turn directly affect the ability of SARS-CoV-2 to infect [43]. A recent study performed on a mice model proposes the modulation of the renin-angiotensin pathways as therapeutic target to protect individuals with SARS from developing acute severe lung failure and acute respiratory distress syndrome [44]. In addition to that, nicotine might exert an anti-inflammatory effect by protecting against the 'cytokine-storm syndrome' responsible of severe SARS-CoV-2 infections [45] [21]. It has been also hypothesized that the cytokine storm, with excessive production of pro-inflammatory molecules, could possibly more easily be triggered in individual who never smoked rather than in smokers, whose immune system is more tolerant and less reactive [46].

Another potential mechanism of action involves nitric oxide (NO) produced during smoking that, due to its reported antiviral effect, might inhibit the virus replication/entry in the cells [21] [47].

Alternatively, from the behavioural perspective, we cannot exclude that smokers, considering themselves at higher risk of developing the disease, were more careful than never smokers in adopting preventative measures, such as physical distancing, hand hygiene, covering coughs, wearing masks when appropriate, having fewer social-relationship, etc. [48].

### 4.1 Limitations and Strengths

The present study has some limitations. Firstly, because of the observational nature of
the study and the cross-sectional design, we cannot infer any causal relationship between smoking habit and COVID-19. In addition, a misclassification of the outcome of severity may exist, since some cases (although numerically limited) might have worsened their conditions a few days after the survey with a subsequent potential distortion of measures of association. Secondly, smoking habit was self-reported therefore recall bias might have led to misclassification of the exposure. Thirdly, the sample was self-selected and not entirely representative of the Italian population because restricted to relatively younger, females, highly educated, and relatively healthy participants, therefore results should be treated with caution when generalized to different populations [49]. Moreover, the low percentage of asymptomatic subjects in our sample may have influenced the evaluation of smoking habit effect on asymptomatic NPS positive subjects. Nevertheless, in a previous study smokers were proportionally represented in asymptomatic patients [50]. Lastly, although we controlled for several potential confounders, we cannot completely rule out the possibility of residual confounding due to unmeasured factors (e.g. passive smoking). Our study has also several strengths. The first one was that evaluating the effect of smoking was the primary goal of the work. The presence in our study sample of subjects from a general population with negative NPS test allows an internal control group (NPS negative individuals). The web-survey reached a large sample of adults with an acceptable geographical coverage reflecting the distribution of SARS-CoV-2 infection in the study period[ CITATION Sel \l 1040 ] and a proportion of smokers that is almost overlapped with the prevalence of current smoking in the Italian population. Finall, and differently from previous published works, we recorded factors not easy to obtain from medical records of inpatients such as the exhaustive details regarding smoking habits (distinguishing between former, active, or never-smokers) and those suspected to play a role of confounders in the observed association, i.e. the socioeconomic status, clinical,
behavioural, and environmental characteristics.

Conclusions

In summary, we are aware that our findings must be carefully evaluated. This article takes as its premise the need to strengthen prevention actions of the most powerful human carcinogen known, which is also a heavy risk factor for many non-communicable diseases [51] and for disease progression in COVID-19 patients. However, we are now facing a second pandemic wave requiring to consider each issue still unresolved on possible role played by smoking in COVID-19 disease. Further researches on the mechanisms of interaction between tobacco smoke exposure and SARS-CoV-2 infection are warrants to fill this knowledge gap.

Abbreviations

Coronavirus disease - COVID-19
Angiotensin-converting enzyme 2 - ACE2
Severe Acute Respiratory Syndrome-Coronavirus-2 - SARS-CoV-2
Nasopharyngeal swab - NPS
European Union General Data Protection Regulation - EU GDPR
Standard deviations - SD
Analysis of variance - ANOVA
Odds Ratios - OR
95% Confidence Intervals - 95%CI
Cardiovascular disease - CVD
Nitric oxide - NO
Captions

Title: Figure 1. Flow-chart of the study population. EPICOVID19: Italian National Epidemiological Survey on COVID-19.

Title: Figure 2. Adjusted odds ratios° and relative 95%CI for smoking status and intensity and duration (N=6,857).

Legend: °Age, sex, education, occupation, area of residence, heart diseases, lung diseases, hypertension, metabolic and oncological diseases, contact with confirmed or suspected COVID-19 cases, living area, crowding index, and living with at risk co-habitants. Mild smokers (<10 cig/day and <15 yrs); Moderate smokers (< 10 cigarettes/day for more than 15 years or >10 cigarettes/day for less than 15 years); Heavy smokers (>10 cigarettes/day for more than 5 yrs). Dots and vertical lines indicate ORs and 95%CI.

Title: Figure 3. Adjusted odds ratios* for positive SARS-CoV-2 test by smoke-related variables (intensity, duration, and pack-years of smoking) (N=6,857)

Legend: *Age, sex, education, occupation, area of residence, heart diseases, lung diseases, hypertension, metabolic and oncological diseases, contact with COVID-19 cases, living area, crowding index, and living with at risk co-habitants.
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F.P., F.B., F.A., F.C. conceived, designed, and planned the study. F.P. and F.A. are responsible for the study procedures. F.P. did the statistical analysis and prepared a first draft of the manuscript; F.B., G.D., S.R., F.A., F.C. contributed to draft the manuscript; F.B., F.A. and F.C. supervised the study; G.D., S.R, A.S, N.J., M.G., A.G., S.M., L.B., S.M., M.N., and R.A.I. critically edited and revised the manuscript for important intellectual content. All authors have approved the submitted version (and any substantially modified version that involves the author’s contribution to the study). The corresponding author, F.P., attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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**Competing interest**

All authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

**Ethical approval**

The Ethics Committee of the Istituto Nazionale per le Malattie Infettive I.R.C.C.S. Lazzaro Spallanzani (Protocol No. 70, 12/4/2020) approved the EPICOVID19 study protocol. When they first accessed the on-line platform, the participants were informed of the purpose of the study, the data to be collected, and the methods of storage and filled in the informed consent. Participation was voluntary and no compensation was expected for respondents. The planning conduct and reporting of studies was in line with the Declaration of Helsinki, as revised in 2013. Data were handled and stored in accordance with the European Union General Data Protection Regulation (EU GDPR) 2016/679, and data transfer was safeguarded by encrypting/decrypting and password protection.
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Supplementary Files
Figures
Flow-chart of the study population.

198,822 participants who completed the survey

254 with missing data on years of smoke

198,568 participants with complete data on smoking

191,250 participants who did not perform the NPS test
461 participants without the NPS results

6,857 participants eligible for analysis
Adjusted odds ratios and relative 95% CI for smoking status and intensity and duration (N=6,857).
Adjusted odds ratios* for positive SARS-CoV-2 test by smoke-related variables (intensity, duration, and pack-years of smoking) (N=6,857).
Multimedia Appendixes
Annex 1.
URL: https://asset.jmir.pub/assets/d058dd662634915635a6bc28084a24b9.docx

Supplementary file_cleaned.
URL: https://asset.jmir.pub/assets/a304ae236627bb5f78d7e647131cf544.docx
CONSORT (or other) checklists

STROBEchecklist_27091.
URL: https://asset.jmir.pub/assets/6883aa8b839e4a312369b021fbc30dd7.pdf