Self-reported symptoms of SARS-CoV-2 infection in a non-hospitalized population: results from the large Italian web-based EPICOVID19 cross-sectional survey.

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Abstract

Background: Understanding the occurrence of Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2)-like symptoms in a large non-hospitalized population, when the epidemic peak was occurring in Italy, is of paramount importance but data are scarce.

Objective: Aims of this study were to evaluate the association of self-reported symptoms with SARS-CoV-2 nasopharyngeal swab (NPS) test in non-hospitalized individuals and to estimate the occurrence of COVID-19-like symptoms in a larger non-tested population.

Methods: This is an Italian countrywide self-administered cross-sectional web-based survey on voluntary adults who completed an anonymous questionnaire in the period 13-21 April 2020. The associations between symptoms potentially related to SARS-CoV-2 infection and NPS results were calculated as adjusted odds ratios with 95% confidence intervals (aOR, 95%CI) by means of multiple logistic regression analysis controlling for age, sex, education, smoking habits, and the number of co-morbidities. Thereafter, for each symptom and for their combination, we calculated sensitivity, specificity, accuracy and AUC in a ROC analysis to estimate the occurrence of COVID-19-like infections in the non-tested population.

Results: A total of 171,310 responded to the survey (59.9% females, mean age 47.4 years). Out of the 4,785 respondents with known NPS test result, 4,392 were not hospitalized. Among them, the NPS positive respondents (n=856) most frequently reported myalgia (61.6%), olfactory and/or taste disorders (OTDs, 59.2%), cough (54.4%), and fever (51.9%) whereas 7.7% were asymptomatic. Multiple regression analysis showed that OTDs (aOR 10.3, [95%CI 8.4-12.7]), fever (2.5, 95%CI 2.0-3.1), myalgia (1.5, 95%CI 1.2-1.8), and cough (1.3, 95%CI 1.0-1.6) were associated with NPS positivity. Having two to four of these symptoms increased the aOR from 7.4 (95%CI, 5.6-9.7) to 35.5 (95%CI, 24.6-52.2). The combination of the four symptoms showed an AUC of 0.810 (95%CI 0.795-0.825) in classifying NPS-P, and was applied to the non-hospitalized and non-tested sample (n=165,782). We found that from 4.4% to 12.1% of respondents had experienced symptoms suggestive of COVID-19 infection.

Conclusions: Our results suggest that self-reported symptoms may be reliable indicators of SARS-CoV-2 infection in a pandemic context. A not negligible part (up to 12.1%) of the symptomatic respondents were left undiagnosed and potentially contributed to the spread of the infection.

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Self-reported symptoms of SARS-CoV-2 infection in a non-hospitalized population: results from the large Italian web-based EPICOVID19 cross-sectional survey.

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ABSTRACT

Background

Understanding the occurrence of Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2)-like symptoms in a large non-hospitalized population, when the epidemic peak was occurring in Italy, is of paramount importance but data are scarce.

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Aims of this study were to evaluate the association of self-reported symptoms with SARS-CoV-2 nasopharyngeal swab (NPS) test in non-hospitalized individuals and to estimate the occurrence of COVID-19-like symptoms in a larger non-tested population.

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This is an Italian countrywide self-administered cross-sectional web-based survey on voluntary adults who completed an anonymous questionnaire in the period 13-21 April 2020. The associations between symptoms potentially related to SARS-CoV-2 infection and NPS results were calculated as adjusted odds ratios with 95% confidence intervals (aOR, 95%CI) by means of multiple logistic regression analysis controlling for age, sex, education, smoking habits, and the number of co-morbidities. Thereafter, for each symptom and for their combination, we calculated sensitivity, specificity, accuracy and AUC in a ROC analysis to estimate the occurrence of COVID-19-like infections in the non-tested population.

Results

A total of 171,310 responded to the survey (59.9% females, mean age 47.4 years). Out of the 4,785 respondents with known NPS test result, 4,392 were not hospitalized. Among them, the NPS positive respondents (n=856) most frequently reported myalgia (61.6%), olfactory and/or taste disorders (OTDs, 59.2%), cough (54.4%), and fever (51.9%) whereas 7.7% were asymptomatic. Multiple regression analysis showed that OTDs (aOR 10.3, [95%CI 8.4-12.7]), fever (2.5, 95%CI 2.0-3.1), myalgia (1.5, 95%CI 1.2-1.8), and cough (1.3, 95%CI 1.0-1.6) were associated with NPS positivity.

Having two to four of these symptoms increased the aOR from 7.4 (95%CI, 5.6-9.7) to 35.5 (95%CI, 24.6-52.2). The combination of the four symptoms showed an AUC of 0.810 (95%CI 0.795-0.825) in classifying NPS-P, and was applied to the non-hospitalized and non-tested sample (n=165,782). We found that from 4.4% to 12.1% of respondents had experienced symptoms suggestive of COVID-19 infection.

Conclusions

Our results suggest that self-reported symptoms may be reliable indicators of SARS-CoV-2 infection in a pandemic context. A not negligible part (up to 12.1%) of the symptomatic respondents were left undiagnosed and potentially contributed to the spread of the infection.

Key words: SARS-CoV-2; COVID-19, voluntary respondents; web-based survey; self-reported symptoms; nasopharyngeal swab testing

INTRODUCTION

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that started in late December 2019 in the Hubei province of China caused millions of cases worldwide in just a few months, and evolved into a real pandemic[1,2]. As of June 25th, 2020, there were 239,706 confirmed cases and 34,678 reported deaths in Italy[3].

It is worth noting that only approximately 20% of SARS-CoV-2 infected patients required hospital care[4]. The vast majority experience mild or subclinical form of the disease did not require hospital admission[5] and a relatively high percentage (40 to 45%) remained asymptomatic[6].

Fever, upper respiratory symptoms, myalgia, headache, and gastrointestinal disturbances have been frequently reported[4,7], as well as the olfactory and taste disorders (OTDs), by SARS-CoV-2 patients[8]. Nevertheless, the prevalence of COVID-19 related symptoms in the population of non-hospitalized is still poorly investigated[9,10]. An early recognition of the conditions attributable to the infection is of paramount importance. This is particularly relevant for identifying promptly not only cases with severe clinical course but also the ones with milder symptomatology who can spread the infection, and who need to be immediately quarantined while testing and contact tracing is carried out.

This study is based on EPICOVID19, an anonymised self-administered web-based survey aimed at estimating the number of suspected cases of COVID-19 and investigating the role of the potential determinants of SARS-CoV-2 infection in a large Italian sample of respondents living in Italy during the lockdown (started in Italy on 9 March 2020). The aims of this paper are to evaluate the association of self-symptoms with SARS-CoV-2 nasopharyngeal swab (NPS) test in non-hospitalized individuals, and to estimate the occurrence of COVID-19-like symptoms in the non-tested population.

METHODS

Study design and setting

EPICOVID19 is a national Italian internet-based survey that was carried out using a cross-sectional research design by a working group dedicated to collaborative public health SARS-CoV-2 research. The survey was launched on 13 April 2020 and targeted adult volunteers living in Italy during the lockdown.

Recruitment

In order to enrol as many subjects as possible, the survey was promoted using social media (Facebook, Twitter, Instagram, Whatsapp), press releases, internet pages, local radio and TV stations, and institutional websites that called upon volunteers to contact the study website[11]. The inclusion criteria were i) age of ≥18 years; ii) access to a mobile phone, computer, or tablet with internet connectivity; and iii) on-line consent to participate in the study.

Development of the web-based questionnaire

EPICOVID19 was developed by the working group after a literature review of existing research into COVID-19, starting with the WHO protocols[12], and of the standard and validated instruments previously used to investigate severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome (MERS)[13,14].

The questionnaire was adapted to the national context and implemented using the European Commission's open-source official EUSurvey management tool[15]. The participants were asked to complete the self-administered 38-item questionnaire, which contained mainly mandatory and closed questions divided into six sections: i) socio-demographic data; ii) clinical evaluation; iii) personal characteristics and health status; iv) housing conditions; v) lifestyle; and vi) behaviours following the lockdown (see Annex 1).

Data collection and variables

For the purposes of this study, we analysed a sub-set of data collected between 13 and 21 April 2020. The socio-demographic information included sex (male *vs* female), age (18-30, 30-39, 40-49, 50-59,

60-69, 70-79, and 80+ years), educational level (primary school or less, middle or high school, and university degree or post-graduate), and occupational status (unemployed, employed, retired, student, and other). Smoking habits were classified as never, former and current smoking. A new variable was created by summing the chronic conditions referred by participants, including lung diseases, heart diseases, hypertension, kidney diseases, immune system diseases, tumours, metabolic diseases, liver diseases, and depression and/or anxiety (categorised as none, 1, 2 or ≥3 co-morbidities). The SARS-CoV-2 related symptoms included: fever of >37.5° for at least three consecutive days; headache, chest pain, myalgia, OTDs, shortness of breath, and feelings of having a fast-beating; gastrointestinal disturbances, including nausea, vomiting and diarrhoea; conjunctivitis; sore throat, rhinorrhoea, and cough (all dichotomised as present/absent). The month of onset of the first symptoms (February/March/April 2020), results of NPS tests (categorised as not done, done with a negative result, done with a positive result, and done with an unknown result), and hospitalisation for confirmed or suspected SARS-CoV-2 infection (dichotomised as yes/no) were also collected.

Study groups definitions

For the aims of this study, we defined three study samples:

1. Sample A, including the total population of respondents (N=171,310);
2. Subsample B, including the non-hospitalized individuals and NPS tested with known result (n=4,392);
3. Subsample C, including the non-hospitalized and non-tested individuals (n=165,782).

Statistical analysis

The continuous variables were expressed as mean values with standard deviations (SD), and the categorical variables as counts and percentages. The χ^2 test and one-way analysis of variance (ANOVA) were used to compare the characteristics of respondents by NPS test result (sample A). The geographical coverage of the sample was evaluated by calculating response rates by Italian region standardized by the number of residents aged ≥18 years on 1 January 2019[16]. When

analysing subsample B we calculated the matrix of pairwise tetrachoric correlations of self-reported symptoms, given the dichotomous nature of these variables. Crude and adjusted logistic regression models, controlling for age, sex, education, smoking habits, and the number of co-morbidities were applied to assess the measurements of association between self-reported symptoms and SARS-CoV-2 NPS positivity versus negativity by estimating the odds ratios (aOR) and 95% Confidence Intervals (CI). Subsequently, a numerical variable including all of those symptoms significantly associated with NPS positivity was created and included in the logistic regression model instead of the single symptoms. Age- and sex-stratified analyses were also performed. In a sensitivity analysis we excluded the respondents who reported February as the month of symptom onset in order to avoid the possible confounding by influenza-like illness (the peak of the Italian flu season 2019-2020 was from January 27th to February 2nd)[17]. Finally, after assessing sensitivity (Se), specificity (Sp) and the Area Under Curve (AUC) in a Receiver Operating Characteristic (ROC) analysis, the symptoms significantly associated with NPS-P were combined as a proxy of COVID-19-like infection in subsample C. All of the statistical analyses were carried out using SPSS Statistics software version 25 (IBM Corp., Armonk, NY, USA) and STATA version 15.0 (StataCorp LP., College Station, Texas, USA). Two-tailed *P*-values < .05 were considered statistically significant.

Ethics and consent form

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. 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 means of encrypting/decrypting and password protection.

RESULTS

Characteristics of the respondents

Table 1 summarises the characteristics of the 171,310 respondents who completed the survey between 13 and 21 April 2020 (sample A). They were prevalently female (59.9%); the mean age of the females was 46.8 (SD, 14.2) years and that of the males was 48.2 (SD, 15.0) years, sixty-one percent had a university degree or post-graduate qualification, and most were regularly employed (69.8%). Smokers and ex-smokers accounted for 42.5% of the respondents (40.0% of the females and 46.5% of the males). About two-thirds of the respondents had no chronic condition, and the vast majority (96.9%) did not undergo NPS testing for SARS-CoV-2. Of the 5,317 who did, 1,135 tested positive (NPS-P), 3,650 tested negative (NPS-N), and 532 did not have the result at the time of completing the questionnaire. A total of 170,700 respondents were non-hospitalized.

Table 1. Characteristics of the respondents by sex (N=171,310, sample A)

	Sex at birth					
	Females		Males		Total	
	n	%	n	%	n	%
Age class, years						
18-30	13,538	13.2	8,611	12.5	22,149	12.9
30-39	21,002	20.5	13,351	19.4	34,353	20.1
40-49	22,907	22.3	14,412	21.0	37,319	21.8
50-59	23,815	23.2	14,941	21.7	38,756	22.6
60-69	16,088	15.7	11,710	17.0	27,798	16.2
70-79	4,386	4.3	4,938	7.2	9,324	5.4
80+	807	0.8	804	1.2	1,611	0.9
Age in years, *mean SD*	46.8	14.2	48.2	15.0	47.4	14.5
Education						
Primary school or less	5,036	4.9	4,005	5.8	9,041	5.3
Middle or high school	33,049	32.2	24,637	35.8	57,686	33.7
University degree or post-graduate	64,458	62.9	40,125	58.3	104,583	61.0
Occupational status						
Unemployed	5,632	5.5	2,136	3.1	7,768	4.5
Employed	70,577	68.8	49,008	71.3	119,585	69.8
Retired	12,281	12.0	10,594	15.4	22,875	13.4
Student	7,196	7.0	4,757	6.9	11,953	7.0
Other	6,857	6.7	2,272	3.3	9,129	5.3
Smoking habit						
Never smokers	61,594	60.1	36,787	53.5	98,381	57.4
Former smokers	22,017	21.5	18,986	27.6	41,003	23.9
Current smokers	18,932	18.5	12,994	18.9	31,926	18.6
Number of co-morbidities						
None	66,294	64.6	44,887	65.3	111,181	64.9
One	27,016	26.3	17,562	25.5	44,578	26.0
Two	7,099	6.9	4,841	7.0	11,940	7.0
Three or more	2,134	2.1	1,477	2.1	3,611	2.1
Molecular test for SARS-CoV-2						
Not done	99,084	96.6	66,909	97.3	165,993	96.9
Done, with a negative result	2,440	2.4	1,210	1.8	3,650	2.1
Done, with a positive result	668	0.7	467	0.7	1,135	0.7
Done, with unknown result	351	0.3	181	0.3	532	0.3
Hospitalized for suspected/confirmed SARS-CoV-2 infection	328	0.3	282	0.4	610	0.4
Not hospitalized, with known molecular test result	2,931	2.9	1,461	2.1	4,392	2.6
All	**102,543**	**59.9**[a]	**68,767**	**40.1**[a]	**171,310**	**100**[a]

[a]*Row percentage*

If unspecified, percentages are column%.

Six hundred and ten respondents (0.35%) said that they had been hospitalised between 1 February and 21 April 2020, including 399 of the 5,317 who were tested for SARS-CoV-2 infection (7.5%) (**Supplementary Table S1**). Females and younger respondents were less likely to be NPS-P, whereas those with a lower level of education or retired were more frequently NPS-P. Current smokers were less prevalent among the subjects with a positive NPS test (9.5%).

Geographical coverage

Although it lacked a formal sampling strategy, the survey reached a large number of subjects throughout Italy. **Figure 1** shows the standardized response rates and the incidence of SARS-CoV-2 infection per 100,000 inhabitants by Italian region as of 23 April 2020[16,18]. As expected, response rates were higher in the northern regions (Lombardy and Piedmont) and reflected the incidence of confirmed cases at that time.

Self-reported symptoms

Figure 2 shows that 68,337 respondents (39.9%) indicated no symptoms. The most frequently reported symptoms were sore throat/rhinorrea (32.9%), headache (27.7%), myalgia (19.2%), gastrointestinal disturbances (16.5%), conjunctivitis (9.3%), and fever (8.0%) (sample A). The absence of symptoms was less frequent among the NPS-P than the NPS-N respondents (6.2% *vs* 30.1%), and there were also notable between-groups differences in the frequency of fever (61.0% *vs* 16.4%), OTDs (58.5% *vs* 8.7%), myalgia (60.8% *vs* 27.8%), cough (57.5% *vs* 28.7%), headache (53.8% *vs* 34.7%) and gastrointestinal symptoms (44.8% *vs* 23.6%). In 102,973 symptomatic subjects, the mean number of symptoms was 5.05 among NPS-P, 3.55 among those with unknown results, 3.16 among NPS-N, and 2.57 among subjects who did not perform the molecular test ($P<.001$).

In the tetrachoric correlation analysis between symptoms (**Supplementary Table S2**) performed in subsample B, values >.6 of the correlation coefficient resulted in the subgroup of symptoms including fever, OTDs, cough and myalgia, whilst values <.3 were mainly observed for sore

throat/rinhorrea and conjunctivitis. In the same subsample B, from univariate and multiple logistic regression analysis controlling for sex, age, education, smoking habits and the number of comorbidities, all of the considered symptoms resulted positively associated with NPS-P (**Table 2**). In the final multiple regression model, with all symptoms included, OTDs (aOR 10.32, [95%CI, 8.39-12.70]), fever (2.46, 95%CI, 1.98-3.05), myalgia (1.45, 95%CI, 1.17-1.80) and cough (1.28, 95%CI, 1.03-1.58) resulted significantly associated with NPS-P. Age per each additional year (1.02, 95%CI, 1.01-1.03) and male sex (1.34, 95%CI, 1.11-1.63) also had increased odds of a positive test, whereas current smoking (0.66, 95%CI, 0.50-0.87) was associated with decreased odds (data not shown). After adding the composite variable of fever, myalgia, cough and OTD to the model and simultaneously adjusting for the other symptoms, we found a strong positive and statistically significant association. The corresponding aORs for the presence of one, two, three and four of these symptoms were respectively 2.66 (95%CI, 2.03-3.49), 7.35 (95%CI, 5.57-9.70), 18.55 (95%CI, 13.77-24.97), and 35.50 (95%CI, 24.60-51.24).

Table 2. Odds ratios of positive molecular test in non-hospitalized respondents with known molecular test results (n=4,392, subsample B)

	Negative		Positive		Model 1	Model 2	Model 3	
	n=3,536	pct=80.5[a]	n=856	pct=19.5[a]	OR (95% CI)[1]	aOR (95% CI)[2]	aOR (95% CI)[3]	*P*-value
Fever	518	14.6	444	51.9	6,28 (5,33-7,39)	6,08 (5,15-7,17)	2.46 (1.98-3.05)	<.001
Myalgia	961	27.2	527	61.6	4,29 (3,67-5,02)	4,33 (3,69-5,07)	1.45 (1.17-1.80)	.001
Olfactory and/or taste disorders	291	8.2	507	59.2	16,20 (13,51-19,42)	16,98 (14,07-20,48)	10.32 (8.39-12.70)	<.001
Cough	984	27.8	466	54.4	3,10 (2,66-3,61)	3,09 (2,65-3,61)	1.28 (1.03-1.58)	.02
Shortness of breath	335	9.5	182	21.3	2,58 (2,12-3,15)	2,63 (2,15-3,23)	0.89 (0.67-1.18)	.40
Chest pain	386	10.9	206	24.1	2,59 (2,14-3,12)	2,61 (2,15-3,16)	0.92 (0.70-1.20)	.54
Feelings of having a fast-beating	354	10.0	165	19.3	2,15 (1,75-2,63)	2,21 (1,80-2,72)	0.93 (0.70-1.23)	.61
Gastrointestinal disturbances	817	23.1	382	44.6	2,68 (2,30-3,13)	2,82 (2,40-3,30)	1.20 (0.98-1.48)	.08
Conjunctivitis	351	9.9	156	18.2	2,02 (1,65-2,48)	2,07 (1,68-2,55)	1.11 (0.85-1.45)	.45
Sore throat/rhinorrea	1,332	37.7	415	48.5	1,56 (1,34-1,81)	1,64 (1,40-1,91)	0.87 (0.71-1.07)	.18
Headache	1,213	34.3	485	56.7	2,50 (2,15-2,91)	2,64 (2,26-3,09)	1.18 (0.95-1.45)	.13
Number of symptoms[b]								
None	1,931	54.6	118	13.8	1	1	1	
One	854	24.1	133	15.5	2,55 (1,96-3,31)	2,61 (2,01-3,39)	2.66 (2.03-3.49)	<.001
Two	441	12.5	185	21.6	6,86 (5,33-8,84)	7,06 (5,47-9,12)	7.35 (5.57-9.70)	<.001
Three	222	6.3	239	27.9	17,62 (13,58-22,86)	17,86 (13,71-23,27)	18.55 (13.77-24.97)	<.001
All	88	2.5	181	21.1	33,66 (24,56-46,14)	34,02 (24,71-46,85)	35.50 (24.60-51.24)	<.001

[a] *Row percentage*
[b] *Ordinal variable summing up the presence of fever, myalgia, cough and olfactory and/or taste disorders*
[1] *Crude Odd Ratios*
[2] *Controlling for sex, age, education, smoking habit, and number of co-morbidities*
[3] *Controlling for sex, age, education, smoking habit, and number of co-morbidities; including all symptoms*
If unspecified, percentages are column%. P-values refer to model 3

Excluding the respondents who referred that their first symptom appeared in February in the sensitivity analysis did not substantially change the results (**Supplementary Table S3**).

In **Tables 3** and **4** are shown the results of the sex- and age-stratified multiple regression analyses. OTDs were more closely associated with the odds of a positive test in females (12.10, 95%CI, 9.35-15.67) and subjects aged ≤50 (15.88, 95% CI, 12.10-20.84), whereas fever was more closely associated with NPS-P in males (3.90, 95%CI, 2.72-5.59) and subjects aged ≥50 (3.46, 95%CI, 2.50-4.78).

Table 3. Sex-specific adjusted odds ratios[a] of positive molecular test in non-hospitalized respondents with known molecular test results (n=4,392, subsample B)

	Females n=2,931, pct=66.7[b]						Males n=1,461, pct=(33.3)[b]					
	Negative		Positive				Negative		Positive			
	n=2,376	pct=81.1[b]	n=555	pct=18.9[b]	aOR (95% CI)	*P*-value	n=1,160	pct=79.4[b]	n=301	pct=20.6[b]	aOR (95% CI)	*P*-value
Fever	341	14.4	272	49.0	1.87 (1.42-2.46)	<.001	177	15.3	172	57.1	3.90 (2.72-5.59)	<.001
Myalgia	674	28.4	352	63.4	1.42 (1.08-1.87)	.01	287	24.7	175	58.1	1.42 (0.99-2.06)	.06
Olfactory and/or taste disorders	210	8.8	357	64.3	12.10 (9.35-15.67)	<.001	81	7.0	150	49.8	8.58 (5.92-12.43)	<.001
Cough	667	28.1	306	55.1	1.34 (1.03-1.74)	.03	317	27.3	160	53.2	1.13 (0.79-1.62)	.50
Shortness of breath	239	10.1	131	23.6	0.88 (0.63-1.23)	.45	96	8.3	51	16.9	0.91 (0.54-1.55)	.74
Chest pain	276	11.6	154	27.7	1.04 (0.76-1.44)	.79	110	9.5	52	17.3	0.72 (0.43-1.18)	.19
Feelings of having a fast-beating	279	11.7	129	23.2	0.91 (0.66-1.27)	.60	75	6.5	36	12.0	1.10 (0.62-1.94)	.75
Gastrointestinal disturbances	587	24.7	266	47.9	1.14 (0.88-1.48)	.34	230	19.8	116	38.5	1.34 (0.94-1.92)	.11
Conjunctivitis	244	10.3	112	20.2	1.19 (0.86-1.64)	.29	107	9.2	44	14.6	1.00 (0.61-1.63)	.99
Sore throat/rhinorrea	950	40.0	279	50.3	0.77 (0.60-0.99)	.04	382	32.9	136	45.2	1.06 (0.75-1.49)	.76
Headache	900	37.9	338	60.9	1.09 (0.84-1.42)	.50	313	27.0	147	48.8	1.33 (0.93-1.90)	.11
Number of symptoms[c]												
None	1,288	54.2	73	13.2	1		643	55.4	45	15.0	1	
One	566	23.8	85	15.3	2.81 (2.00-3.96)	<.001	288	24.8	48	15.9	2.39 (1.53-3.72)	<.001
Two	306	12.9	112	20.2	7.13 (5.00-10.16)	<.001	135	11.6	73	24.3	7.95 (5.06-12.47)	<.001
Three	150	6.3	162	29.2	20.35 (14.00-29.57)	<.001	72	6.2	77	25.6	15.30 (9.29-25.22)	<.001
All	66	2.8	123	22.2	35.28 (22.44-55.47)	<.001	22	1.9	58	19.3	39.65 (20.69-76.00)	<.001

[a]*After controlling for sex, age, education, smoking habit, and number of co-morbidities*
[b]*Row percentage*
[c]*Ordinal variable summing up the presence of fever, myalgia, cough and olfactory and/or taste disorders*
If unspecified, percentages are column%.

Table 4. Age-specific adjusted odds ratios[a] of positive molecular test in non-hospitalized respondents with known molecular test results (n=4,392, subsample B)

	Age <50 n=2,659, pct=60.5[b]						Age ≥50 n=1,733, pct=39.5[b]					
	Negative		Positive				Negative		Positive			
	n=2,176	pct=81.8[b]	n=483	pct=18.2[b]	aOR (95% CI)	*P*-[b]	n=1,36[b]	pct=78.5[b]	n=37[b]	pct=21.5[b]	aOR (95% CI)	*P*-[b]
Fever	341	15.7	239	49.5	1.98 (1.47-2.65)	<.001	177	13.0	205	55.0	3.46 (2.50-4.78)	<.001
Myalgia	599	27.5	308	63.8	1.61 (1.20-2.18)	.002	362	26.6	219	58.7	1.35 (0.98-1.86)	.07
Olfactory and/or taste disorders	177	8.1	323	66.9	15.88 (12.10-20.84)	<.001	114	8.4	184	49.3	5.25 (3.75-7.34)	<.001
Cough	639	29.4	266	55.1	1.14 (0.85-1.53)	.37	345	25.4	200	53.6	1.39 (1.02-1.91)	.04
Shortness of breath	223	10.2	117	24.2	0.90 (0.62-1.31)	.58	112	8.2	65	17.4	0.79 (0.51-1.23)	.29
Chest pain	267	12.3	133	27.5	0.95 (0.67-1.35)	.76	119	8.8	73	19.6	0.90 (0.59-1.38)	.63
Feelings of having a fast-beating	243	11.2	101	20.9	0.80 (0.55-1.17)	.25	111	8.2	64	17.2	1.12 (0.73-1.73)	.60
Gastrointestinal disturbances	543	25.0	231	47.8	1.33 (1.00-1.76)	.048	274	20.1	151	40.5	1.14 (0.83-1.57)	.42
Conjunctivitis	198	9.1	80	16.6	0.93 (0.64-1.36)	.71	153	11.3	76	20.4	1.34 (0.92-1.97)	.13
Sore throat/rhinorrea	918	42.2	272	56.3	0.89 (0.68-1.17)	.41	414	30.4	143	38.3	0.85 (0.63-1.16)	.31
Headache	837	38.5	300	62.1	1.23 (0.92-1.63)	.16	376	27.6	185	49.6	1.21 (0.88-1.65)	.24
Number of symptoms[c]												
None	1,167	53.6	52	10.8	1		764	56.2	66	17.7	1	
One	521	23.9	80	16.6	3.70 (2.54-5.41)	<.001	333	24.5	53	14.2	1.83 (1.23-2.73)	.003
Two	285	13.1	101	20.9	8.91 (6.03-13.15)	<.001	156	11.5	84	22.5	6.20 (4.14-9.30)	<.001
Three	147	6.8	146	30.2	24.39 (16.19-36.75)	<.001	75	5.5	93	24.9	13.98 (8.92-21.90)	<.001
All	56	2.6	104	21.5	45.86 (27.94-75.29)	<.001	32	2.4	77	20.6	26.27 (14.95-46.17)	<.001

[a]*After controlling for sex, age, education, smoking habit, and number of co-morbidities*
[b]*Row percentage*
[c]*Ordinal variable summing up the presence of fever, myalgia, cough and olfactory and/or taste disorders*
If unspecified, percentages are column%.

After dichotomizing for the presence of two or more and of three or more, the resulting aORs were 12.17 (95%CI, 9.50-15.59) and 22.44 (95%CI, 16.93-29.75). When the four symptoms were singularly analyzed, the larger AUC (0.749, 95%CI 0.730-0.767) was found for OTDs, characterized also by better Sp=91.8%, with myalgia having the higher sensitivity (Se=61.6%) in classifying NPS-P. The combination of the four symptoms increased the AUC to 0.810 (95%CI 0.795-0.825), with higher sensitivity at the cut-off of two or more (Se=70.7) and higher specificity at the cut-off of three or more (Sp=91.2%) (data not shown).

As a final step, we quantified the amount of probable SARS-CoV-2 infections in the non-hospitalized and non-tested population (subsample C) by calculating the frequencies for the combination of the four symptoms resulted from the analysis on subsample B. We found that, with an accuracy of 77.2% and 83.0% respectively, 20,103 respondents (12.1%, 95%CI 12.0%-12.3%) had two or more and 7,739 ones (4.4%, 95%CI 4.3%-4.6%) had three or more symptoms suggestive of novel coronavirus disease.

DISCUSSION

This study, based on the responses of >170,000 persons to a web-based survey, outlined the COVID-19 symptom profile of the cases that did not require hospitalisation during the outbreak of the epidemic in Italy. OTDs, myalgia, fever and cough were symptoms associated with laboratory-proven SARS-CoV-2 infection. Among non-hospitalized and non-tested respondents, from 4.4% to 12.1% experienced symptoms suggestive of COVID-19 illness.

Although approximately 60% of the respondents reported at least one symptom compatible with the viral infection, only 3.4% of these had access to NPS testing for SARS-CoV-2. Respondents with at least one symptom accounted for 94% of NPS-P patients, 70% of NPS-N patients, and 75% of the patients with an unknown NPS test result. We here report that sub-groups with symptomatology similar to NPS-P subjects have not been tested, a worrying finding that suggests a large number of cases may have remained undiagnosed or may not have been correctly quarantined[19]. Active case finding with prompt isolation and contact tracing would be a highly important means of ending the

spread of SARS-CoV-2 infection[20], which otherwise likely might continue through households[21]. The very limited number of respondents who were diagnosed based on NPS testing is a consequence of the decision by health authorities to reserve the use of diagnostics for clinically severe cases and creating suboptimal conditions for effective contact tracing.

A number of papers have described the clinical characteristics, symptoms and disease course of SARS-CoV-2 in-patients[22,23] and out-patients[24], but still little is known about the natural history of the infection and its clinical spectrum or rate of symptoms in non-hospitalized COVID-19 cases. In our analyses, we showed a strong association between OTDs and NPS-P, with NSP-P respondents having more than 10-fold increased risk of having OTDs. In line with our findings, OTDs has been reported as symptom specific of SARS-CoV-2 infection in clinical[8,25] and non-clinical setting[9,26,27]. In 18,401 users of “COVID symptom tracker mobile app” in UK and US who underwent molecular testing, loss of smell in addition to fever and persistent cough was found as potential predictor of COVID-19[9]. Similar results were recently reported from two other on-line surveys in Italian[26] and in French population[27]. Consistently with the aforementioned population studies, we also found that other COVID-19 related symptoms as fever, myalgia or cough were significantly associated with NPS-P, even though less specific than OTDs. Overall, the four above-mentioned symptoms demonstrated an additive effect that increases the probability of NPS-P.

Interestingly, our sub-set analyses revealed some associations between the respondents’ symptoms and their demographic characteristics. The association between OTDs and NPS-P was stronger in younger patients, possibly because the known deterioration in the sense of smell during aging[28] means that younger subjects are more likely to notice its loss. We also found that NSP-P was more closely associated with OTDs in women and with fever in men, although both symptoms are significantly associated with NSP-P in both sexes. The association between female and OTDs has also been reported in hospitalized COVID-19 patients[8].

Notably, in the subpopulation of 165,782 participants who were not NPS-tested and non-

hospitalized, we calculated with accuracy close to 80% that 12.1% had two or more of these symptoms and 4.4% had three or more, leading to a significant number of adults with COVID-19-like illness. Applying the most conservative criterion (presence of three or more symptoms at the same time), characterized by a specificity of 91.2%, we estimated that about 2.2 millions of Italian adults had high probability of being COVID-19 symptomatic cases up to April 21, 2020.

The estimation of the real proportion of the population infected is a fundamental indicator for public health policy makers in the ongoing COVID-19 pandemic. During the epidemic peak, model-based estimates[29] have suggested that the ratio between notified and actual cases ranges from 1:5 to 1:20, but to date in Italy real-world data are limited to restricted local settings or are available only in case of NPS testing of symptomatic patients with serious illness and requiring intensive or sub-intensive medical care. This lack has led to a wide underestimation of the spread of novel coronavirus in the mild symptomatic individuals or in those with limited access to testing. For this reason, our results seem to be quite and consistent with other surveys performed in large populations. A model combing symptoms to predict probable infection was applied to the data derived from the “COVID symptom tracker mobile app” in UK and USA[9], indicating that the 17.4% users were likely to have COVID-19-like infection. Data from a nationally representative survey of Canadian indicated that about 8% of adults reported they or someone in their household had symptoms suggestive of novel coronavirus disease in March 2020[10].

These findings suggest that during a pandemic, when testing and contact tracing should be prioritized, the presence of such symptoms, also detected through a simple anamnestic investigation, may be an early indicator of SARS-CoV-2 infection in individuals who should be quarantined and molecularly tested.

It is also interesting to note that 7.7% of non-hospitalized patients with a NPS-P test reported no symptoms. A number of studies have suggested that asymptomatic patients may be virus spreaders[30,31]. According to the results from sixteen SARS-CoV-2 testing studies pooled by Oran and colleagues, asymptomatic persons accounted for approximately 40% to 45% of COVID-19

infections[6]. In the Italian population study carried out on about 2,500 residents in the municipality of Vo', authors showed that the age-adjusted prevalence of COVID-19 asymptomatic cases was 43.2% (95CI 32.2%-54.7%)[5]. The characteristics of our study make it unsuitable for precisely estimating the percentage of completely asymptomatic, and our lower-than-expected findings can be explained by the limited access to molecular testing for the asymptomatic individuals and by the possible over-reporting of symptoms.

Our data concerning an apparently protective role of smoking in relation to NPS-P add new evidence to a panorama in which it has been suggested that this habit may have divergent clinical, prognostic and epidemiological effects in COVID-19 patients[32]. This issue will be investigated in more detail in a separate article in order to contribute further to the current debate[33].

Study limitations and strengths

Given the voluntary nature of the survey, it was not intended to assess a representative sample of the general population. However, extensive participation has allowed us to collect a sample that is quite balanced in terms of gender and age, although more shifted towards younger subjects with a higher level of education as can be expected in the case of an on-line questionnaire. The characteristics of a web-based survey may have also introduced a bias leading people with symptoms to respond more often than those without symptoms, and people who are health-conscious to exacerbate (over-report) their symptoms. In addition, some symptoms (e.g OTDs) are more likely to be subjected to recall bias due to media emphasis on their association with the disease.

At the date of the survey collection analysis the NPS "testing rate" among Italian adults (age≥18 years) was 1.92%[3] versus 3.10% among responders to EPICOVID19, suggestive of a greater propensity to participate for individuals who felt at higher risk, for symptomatology or closeness to COVID-19 cases. On 21st April the total number of SARS-CoV-2 cases in Italy was 183,957[3] out of the 971,246 individuals who underwent the NPS test, with a NPS-positive cumulative prevalence rate equal to 18.9%, similarly to the rate of 23.7% observed in our study. By that time, in Italy the cumulative number of hospitalized COVID-19 patients was 78,205, and the number of deceased

due to novel coronavirus (unknown if hospitalized) was 24,648. The cumulative prevalence rate of hospitalized COVID-19 cases therefore ranged 0.15%-0.20% among the Italian adults. The total number of hospitalized EPICOVID19 respondents (for suspect or confirmed COVID-19 illness) was 610 (0.36%), among these 279 (0.16%) were NPS-P, in line with the hospitalization rates in the general population.

As the sample was self-selected the generalisability of our results should be done with caution. Lastly, a single self-reported negative test cannot exclude a possible SARS-CoV-2 infection.

On-line surveys have become an accepted, low-cost and scalable means[34,35] of efficiently and rapidly involving a large number of people regardless of geographical distance, thus making them somehow preferable to more traditional, time-consuming and expensive methods, especially in an ongoing emergency situation. Further, in the context of this outbreak the EPICOVID19 survey might have involved people who had no opportunity to report their symptoms in other ways. It is noteworthy that our survey achieved a satisfactory geographical coverage, proportional, as expected, to the distribution of COVID-19 infection and to the reasonable likelihood that communities living in more affected areas would be more willing to respond.

To the best of our knowledge, this is the largest Italian web-based survey of SARS-CoV-2 symptoms and, notably, carried out during the epidemic peak in Italy, when data at population level were unavailable. National authorities, healthcare workers and the public have known little about the real spread of the infection since it started. Our preliminary findings shed some light on paucisymptomatic or mild infections by novel coronavirus disease in Italy.

Conclusions

The adoption of effective strategies and ready-to-use digital tools, like the real-time reporting internet-based EPICOVID19, aimed at ascertaining the positivity of paucisymptomatic carriers is still urgently needed in Italy and worldwide. The implementation of these strategies is fundamental also in countries, like the European ones, where the spread of the infection is currently declining but programs of active surveillance are necessary to reduce the risk of a new SARS-CoV-2 outbreak in

the future. Many individuals with COVID-like infection are destined to remain beyond the control of the health authorities, thus representing an important source for the further spread of the infection. The determination of a symptomatic profile capable of easily identifying a suspected case may greatly contribute to contain the pandemic. Although they are also associated with other respiratory tract infections, the simultaneous presence of symptoms such as fever, cough, myalgia and OTDs revealed by this study seems to be associated with a high probability of carrying active SARS-CoV-2 infection in a pandemic context.

Abbreviations

Severe Acute Respiratory Syndrome-Coronavirus-2 - SARS-CoV-2

Olfactory and/or taste disorders - OTDs

Nasopharyngeal swab – NPS

Severe acute respiratory syndrome – SARS

Middle Eastern respiratory syndrome – MERS

Standard deviations – SDs

Adjusted Odds Ratios – aOR

95% Confidence Intervals - 95%CI

European Union General Data Protection Regulation - EU GDPR

NPS positivity - NPS-P

NPS negativity - NPS-N

Sensitivity – Se

Specificity – Sp

Area Under Curve – AUC

Receiver Operating Characteristic - ROC

Figure 1. Title: Comparison of survey response rates and the incidence of SARS-CoV-2 infection per 100,000 inhabitants by Italian region.

Legend: Left**:** response rates x100,000. Right: incidence rates of SARS-CoV-2 x100,000.

Figure 2. Title: Self-reported symptoms in 171,310 respondents by SARS-CoV-2 molecular test.

Legend: Error bars are ±2*standard error (normal approximation).

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Contributors

FA and FP contributed equally to this paper. FA and FP had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. MG, FA, FP, FB, AG, GP, SR, RAI, and MT conceptualized and designed the study. MG, FP, FA, FB, AG, and GP drafted the manuscript. FA and FP analysed the data. SR, SMa, CT, MN, SMo, LB, AS, NJ, CP, DB, MT, MA, CM, RAI critically revised the manuscript for important intellectual content. NJ and LF provided technical and material support. RAI, SMa and MG supervised the study. All authors participated in data interpretation, read, and approved the final version.

The corresponding author, MG, attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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None

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.

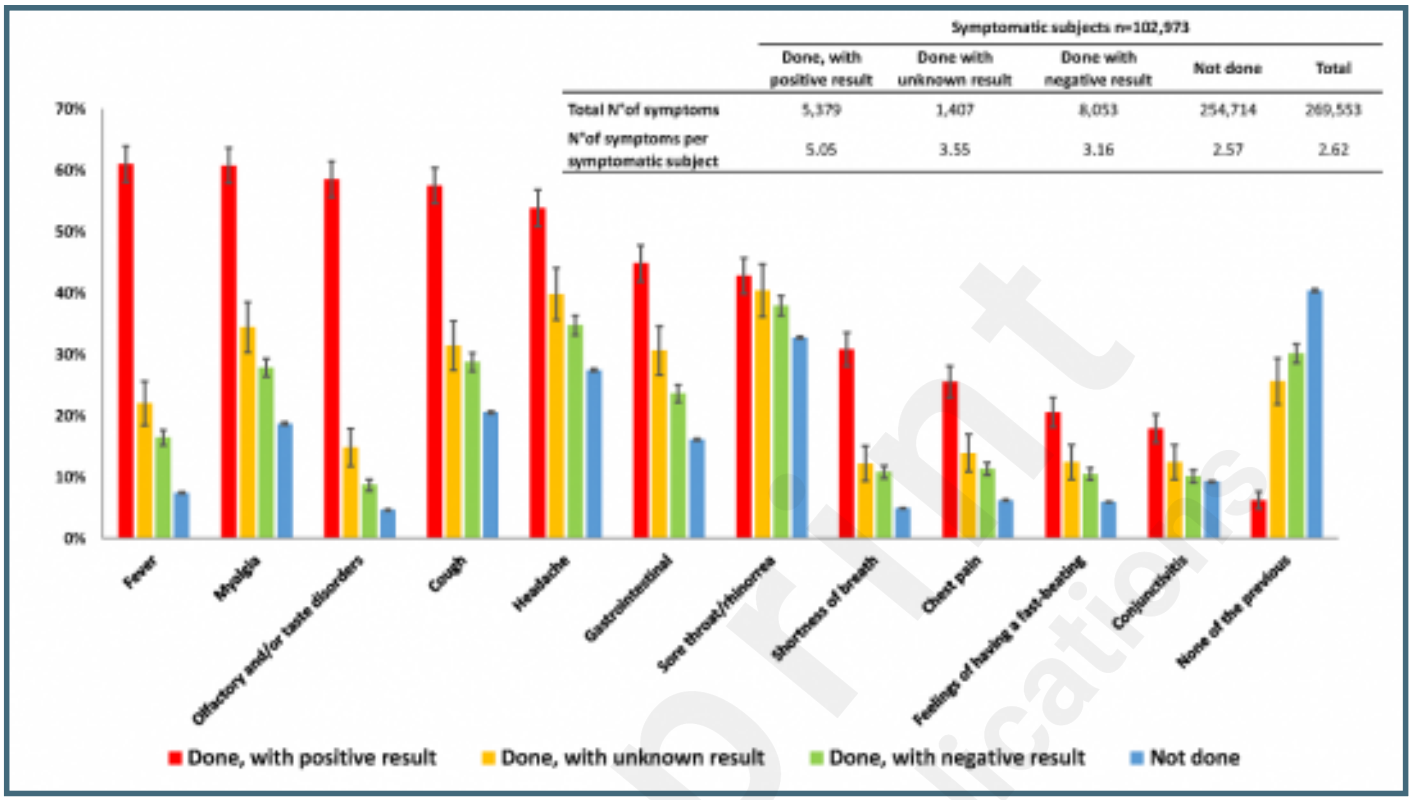
Ethical approval

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. The planning conduct and reporting of studies was in line with the Declaration of Helsinki, as revised in 2013.

Supplementary Files

Figures

Title: Self-reported symptoms in 171,310 respondents by SARS-CoV-2 molecular test. Legend: Error bars are ±2*standard error (normal approximation).



Title: Comparison of survey response rates and the incidence of SARS-CoV-2 infection per 100,000 inhabitants by Italian region. Legend: Left: response rates x100,000. Right: incidence rates of SARS-CoV-2 x100,000.