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Day-by-day symptoms following positive and negative PCR tests for SARS-CoV-2 in non-hospitalized healthcare workers: A 90-day follow-up study

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ABSTRACT

Objective: Our study aimed to compare symptoms day by day for non-hospitalized individuals testing positive and negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
Methods: In total, 210 positive-test and 630 negative-test healthcare workers in the Central Denmark Region were followed for up to 90 days after testing, between April and June, 2020. Their daily reported COVID-19-related symptoms were compared graphically and by logistic regression.
Results: Thirty per cent of the positive-test and close to 0% of the negative-test participants reported a reduced sense of taste and smell during all 90 days (adjusted odds ratio [aOR] 86.07, 95% CI 22.86–323). Dyspnea was reported by an initial 20% of positive-test participants, declining to 5% after 30 days, without ever reaching the level of the negative-test participants (aOR 6.88, 95% CI 2.41–19.63). Cough, headache, sore throat, muscle pain, and fever were temporarily more prevalent among the positive-test participants; after 30 days, no increases were seen. Women and older participants were more susceptible to long-lasting COVID-19 symptoms.
Conclusion: The prevalence of long-lasting reduced sense of taste and smell is highly increased in mild COVID-19 patients. This pattern is also seen for dyspnea at a low level, but not for cough, sore throat, headache, muscle pain, or fever.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected most countries over the last year, leading to the coronavirus disease 2019 (COVID-19) pandemic (European Centre for Disease Prevention and Control, 2020). The clinical manifestations of acute SARS-CoV-2 infection range from asymptomatic, through mild symptoms, to life-threatening infection with

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compromised respiratory capacity and organ failure. Most patients hospitalized with COVID-19 present fatigue, fever, cough, dyspnea, musculoskeletal pain, headache, and reduced sense of taste and smell (Docherty et al., 2020; Guan et al., 2020). A high proportion continue to have symptoms — particularly fatigue, anosmia, sleep difficulties, and musculoskeletal pain — after recovery (Carfì et al., 2020; Dennis et al., 2021; Huang et al., 2021). There is increasing concern about the long-term consequences, with a post-COVID-19 syndrome being discussed (del Rio et al., 2020; Marshall, 2020; NIHR, 2000).

Uncontrolled data from the general population and non-hospitalized COVID-19 patients with mild disease indicate that a high proportion suffer from SARS-CoV-2-related symptoms several weeks after diagnosis (Boscolo-Rizzo et al., 2020; Eythorsson et al., 2020; Murray et al., 2021; Paderno et al., 2020; Reiter et al., 2020; Tenforde et al., 2020). Prospective follow-up studies of non-hospitalized COVID-19 patients, including a reference group accounting for symptoms not attributable to SARS-CoV-2, are warranted (Yelin et al., 2020). The few studies comparing symptom courses of positive-test with those of negative-test non-hospitalized participants show increased occurrence of reduced sense of taste and smell, and several other symptoms that persist for several weeks and months after a positive SARS-CoV-2 test (Cirulli et al., 2020; Mizrahi et al., 2020). The aim of our study was to compare day-by-day symptoms of SARS-CoV-2 PCR positive-test and negative-test non-hospitalized healthcare workers up to 90 days after testing.

Methods

Design and study setting

A prospective follow-up study of healthcare workers and other occupational groups from all hospitals in the Central Denmark Region was carried out from April 24 until June 30, 2020.

Participants

All hospital employees were invited by email to report COVID-19-related symptoms on a day-by-day basis. Participants tested by PCR for SARS-CoV-2 between March 11 and June 30, 2020, at any of the regional hospitals or public testing centres, were identified in the Central Denmark Region business intelligence system. The study included those with at least one daily symptom report from the day they were tested and beyond. Those hospitalized for COVID-19 for more than 24 h were excluded because our focus was non-hospitalized individuals.

PCR test for SARS-CoV-2 RNA

National surveillance of SARS-CoV-2 infection, assessed by reverse transcription PCR-based detection of viral RNA in nasopharyngeal and oropharyngeal swabs, was initiated in Denmark on March 2, 2020 (Statens Serum Institut, 2020a,b). Until March 11, only symptomatic individuals returning from high-risk areas and symptomatic contacts could be tested. From March 12, individuals with severe symptoms, individuals at risk because of high age or comorbidities, or those with critical functions, could also be tested. From April 1, individuals with mild symptoms, and from April 21, close contacts regardless of symptoms, had the opportunity to be tested. From May 18, all adults were offered testing. From April 21, all patients were tested before being admitted to hospital or undergoing high-risk procedures during outpatient visits.

PCR analysis for SARS-CoV-2 RNA was performed in the Clinical Microbiology Department at Aarhus University Hospital, with detection of the ORF-1a/b and E-gene (commercial assay) or exclusively the E-gene, and at the national testing facility at TestCenter Denmark, Statens Serum Institut, with detection of the E-gene, both in-house PCRs in accordance with the Charité protocol recommended by WHO (Corman et al., 2020; Vogels et al., 2020). Automated RNA extraction was performed at both facilities. Internal negative and positive controls were included in both the RNA extraction step and in the reverse transcription PCR step.

Questionnaire

After giving informed consent, participants received a short baseline questionnaire and then a short text message on their mobile phone or by email every day at 3:30 pm, linking to a questionnaire regarding the presence (yes and no) of the following symptoms within the previous 24 h: cough, sore throat, headache, fever, muscle aches and pains, dyspnea, and reduced or lost sense of taste and smell (available in Supplementary data). Participants could respond within 24 h from receiving the message and could resume reporting if they skipped one or more days. Smoking status was collected in the baseline questionnaire.

Other data

Information on occupation, sex, and age was provided by the Business Intelligence institution of the Central Denmark Region.

Statistical analyses

Participants were followed from the date of the first completed questionnaire after the first positive test or first negative test, until the date of the last questionnaire, 90 days after being tested or June 30, whichever came first. No participants had a positive test after a negative test during the follow-up period.

Because the indication for being tested, testing rate, and infection rate in the study population changed rapidly over time (Supplementary Figure S1), for each participant who tested positive, three controls were randomly selected among participants who tested negative and were matched for sex and testing date ($\pm$ 2 days). The three-fold number of controls was defined by the maximum allowed within the narrowest strata. When selecting controls, we avoided crossing the dates when indications for being tested had changed, as specified above.

For positive-test and negative-test participants, the prevalence of the seven symptoms for each day of follow-up was computed. The prevalences were plotted and the curves smoothed using local three-degree polynomial kernels. Standard error-based 95% confidence intervals (95% CI) were obtained based on 100 bootstrap samples, resampling among the positive-test participants and repeating the matching of negative-test participants and the smoothing procedure.

Odds ratios (OR) for any symptom and for the seven specific symptoms were estimated by test result (positive, negative) for three time periods (0–30, 31–60, and 61–90 days) since the test by conditional logistic regression and matched by sex and testing date, as specified above. Whether sex affected symptom prevalence among positive-test relative to negative-test participants was assessed by including an interaction term between test result and sex (male, female). The possible modifying effect of age (<45 years, $\geq$45 years, median age) and testing date ($\leq$April 7, >April 7, median testing date) were similarly assessed. Selection bias was also assessed, i.e., whether positive-test and negative-test participants' questionnaire responses on a given day were modified by the presence of symptoms the previous day, using a model that included test result, any symptom (present and absent), the

interaction term between the two, and responses on the questionnaire (yes and no). The conditional logistic regression models were adjusted for age (<30, 30–39, 40–49, 50–59, and ≥60 years), except analyses of effect modification by age, occupation (nursing staff, medical doctors, biomedical laboratory scientists, medical secretaries, and other), and smoking (current, previous, and never), unless otherwise specified. Overall odds ratios for the entire follow-up period were furthermore adjusted according to time since testing (0–30, 31–60, and 61–90 days). The covariates were decided on an a priori basis. Confidence intervals were obtained by bootstrapping. As described above. Data handling and statistical analyses were performed using Stata 16.1.

Results

Between April 23 and May 5, 32 413 healthcare workers and administrative personnel were invited to participate in day-by-day symptom reporting, and 12 115 (37.4%) accepted. Between March 11 and June 30, 215 respondents were tested as PCR-positive for SARS-CoV-2, and 3421 were tested as PCR-negative. Five of the positive-test and four of the negative-test participants were hospitalized for >24 h on suspicion of COVID-19, and were excluded. Among the remaining 3417 negative-test participants, 630 referents were randomly selected, matched by sex and testing date and representing 447 individuals. The study population therefore included 210 positive-test and 630 negative-test participants. Two referents were selected five times — the maximum number of repeats observed. Data from a mean of 50 positive-test and 164 negative-test participants were included for days 0–30 since testing, 128 and 431, respectively, for days 31–60, and 87 and 300, respectively, for days 61–90.

The sex and testing date distributions were identical for positive-test and negative-test participants, as expected due to the matched design, and with only minor differences in age, smoking habits, and time from testing to responding to the first questionnaire (Table 1). The mean daily response rate declined from 80.9% and 79.1% during days 0–30 for the positive-test and negative-test participants, respectively, to 54.6% and 63.1% during days 61–90. Nursing staff were relatively more prevalent compared with other occupations (e.g., administrative, service, and technical staff, and social workers), with limited patient contact among the positive-test participants.

During the first days after being tested, around 80% of the positive-test and 75% of the negative-test participants reported at least one of the seven symptoms (Figure 1). Ninety days later, these prevalences had gradually declined to about 40% and 10%, respectively. This corresponded with four-fold increased odds ratios for the complete follow-up period (adjusted odds ratio [aOR] 3.79, 95% CI 2.54–5.66) and for each of the three periods since testing (Table 2).

Reduced or lost sense of taste and smell was consistently reported by 30% of the positive-test participants, except for a somewhat higher level during the initial days (Figure 1). Almost none of the negative-test participants reported these symptoms. The odds ratio tended to increase with time since testing, with the overall estimate 80-fold increased (aOR 86.07, 95% CI 22.86–323; Table 2). Dyspnea was reported by an initial 20% of positive-test participants and declined gradually to about 5% after 30 days without ever reaching the level of the negative-test participants (Figure 1). During the first 30 days of follow-up, the odds ratio was 11-fold increased (aOR 10.93, 95% CI 2.29–52.10) compared with negative-test participants. This ratio was reduced over subsequent days with an overall adjusted odds ratio of 6.88 (95% CI 2.41–19.63). Half of the positive-test and 15% of the negative-test participants reported cough during the initial days (Figure 1). The adjusted odds ratio for the first 30 days was 2.19 (95% CI 1.10–4.37).

Table 1
Characteristics of 210 SARS-Cov-2 positive-test and 630 SARS-Cov-2 negative-test participants matched for sex and testing date.

	Positive test	Negative test
Sex		
Female	177 (84.3%)	531 (84.3%)
Male	33 (15.7%)	99 (15.7%)
Testing date		
March 12–31	57 (27.1%)	171 (27.1%)
April 1–20	135 (64.3%)	405 (64.3%)
April 21–May 17	18 (8.6%)	54 (8.6%)
May 18–June 30	0	0
Age, years		
<30	33 (15.7%)	58 (9.2%)
30–39	49 (23.3%)	153 (24.3%)
40–49	64 (30.5%)	221 (35.1%)
50–59	49 (23.3%)	146 (23.2%)
≥60	15 (7.1%)	52 (8.3%)
Number of days from testing to first questionnaire response		
0–30	173 (82.4%)	526 (83.5%)
31–60	37 (17.6%)	103 (16.3%)
61–90	0 (0.0%)	1 (0.2%)
Mean daily response rate since testing (range)		
Days 0–30	80.9% (69–100)	79.1% (70–94)
Days 31–60	63.9% (57–73)	71.1% (64–78)
Days 61–90	54.6% (47–60)	63.1% (58–70)
Occupation		
Nursing staff	140 (66.7%)	290 (46.0%)
Medical doctors	38 (18.1%)	111 (17.6%)
Biomedical laboratory scientists	8 (3.8%)	37 (5.9%)
Medical secretaries	5 (2.4%)	39 (6.2%)
Other[a]	19 (9.0%)	153 (24.3%)
Smoking		
Current smoker	10 (4.8%)	29 (4.6%)
Previous smoker	60 (28.6%)	204 (32.4%)
Never smoker	140 (66.7%)	397 (63.0%)

[a] Administrative, service and technical staff, social workers, and other less prevalent occupations.

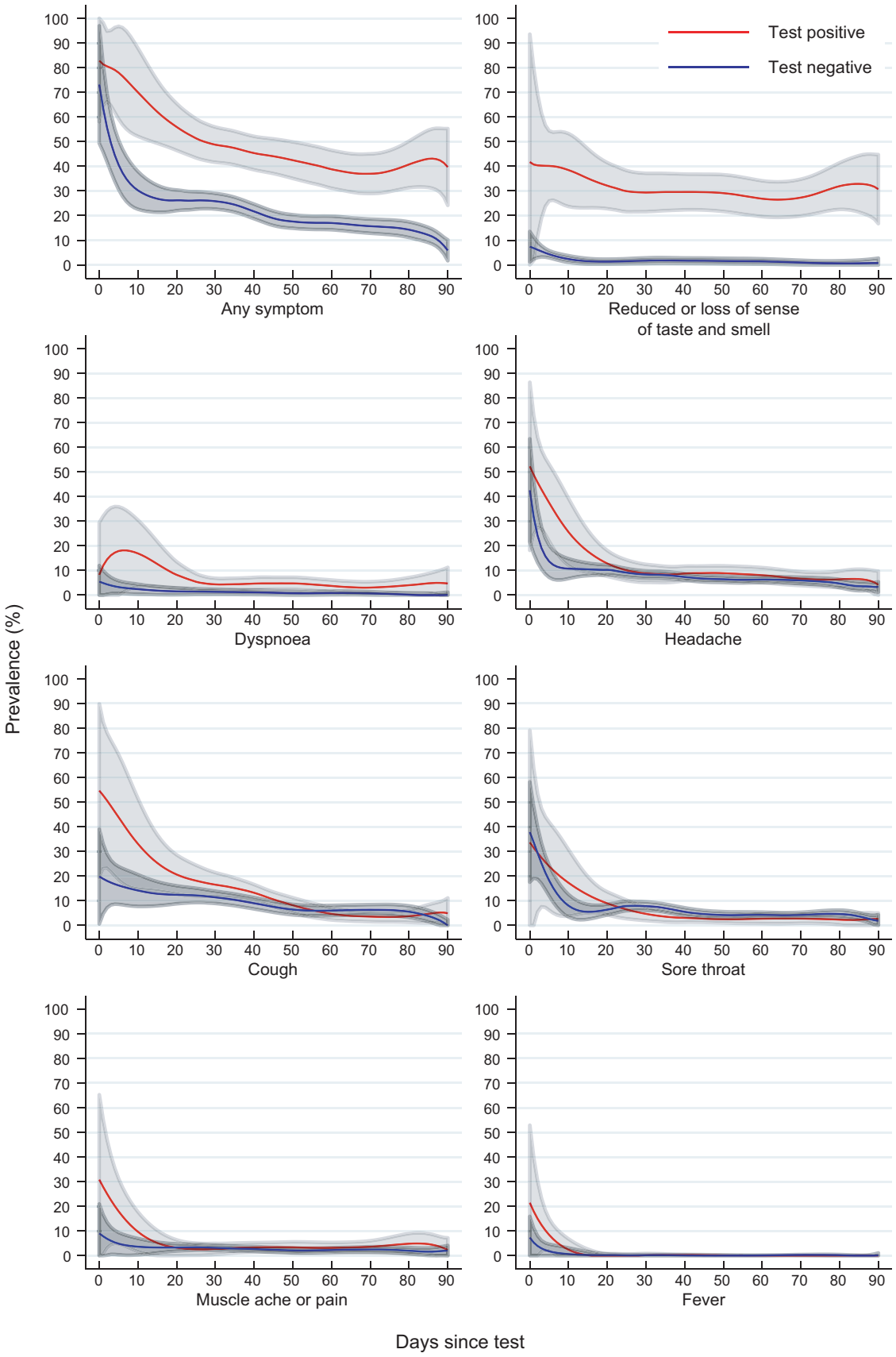

Figure 1. Symptom prevalences (%) by days since SARS-CoV-2 PCR test.
210 participants tested positive and 630 participants tested negative for SARS-CoV-2 and individually matched for sex and testing date. Confidence intervals are shown by the shaded areas.

Table 2
Adjusted odds ratios for seven symptoms by SARS-CoV-2 test result and time since testing.

	Time since testing														
	Days 0–30					Days 31–60					Days 61–90					Day 0–90
	Positive test (173 participants); 1552 daily recordings[a]		Negative test (526 participants); 5096 daily recordings[a]		Adjusted odds ratio (95% CI)[b]	Positive test (181 participants); 3828 daily recordings[a]		Negative test (581 participants); 12 920 daily recordings[a]		Adjusted odds ratio (95% CI)[b]	Positive test (148 participants); 2608 daily recordings[a]		Negative test (515 participants); 8997 daily recordings[a]		Adjusted odds ratio (95% CI)[b]	Adjusted odds ratio (95% CI)[b]
	n	%	*n*	%		*n*	%	n	%		*n*	%	*n*	%		
Any symptom	862	55.5	1426	28.0	4.18 (2.63–6.62)	1689	44.1	2604	20.2	3.59 (2.37–5.44)	1003	38.5	1319	14.7	4.59 (2.44–8.64)	3.79 (2.54–5.66)
Reduced or lost sense of taste and smell	491	31.6	92	1.8	57.16 (16.71–195)	1120	29.3	217	1.7	62.66 (15.15–259)	745	28.6	77	0.9	226.38 (160.23–319)	86.07(22.86–323)
Dyspnea	119	7.7	81	1.6	10.93 (2.29–52.10)	179	4.7	133	1.0	6.76 (1.79–25.47)	92	3.5	48	0.5	6.27 (0.53–73.45)	6.88 (2.41–19.63)
Headache	227	14.6	531	10.4	1.53 (1.00–2.33)	337	8.8	907	7.9	1.34 (0.84–2.13)	172	6.6	480	5.3	1.21 (0.59–2.49)	1.32 (0.81–2.18)
Cough	340	21.9	641	12.6	2.19 (1.10–4.37)	405	10.6	1023	7.9	1.27 (0.75–2.15)	106	4.1	492	5.5	0.81 (0.32–2.08)	1.33 (0.81–2.18)
Sore throat	149	9.6	439	8.6	1.33 (0.77–2.34)	115	3.0	661	5.1	0.60 (0.28–1.27)	72	2.8	364	4.0	0.61 (0.21–1.77)	0.82 (0.46–1.48)
Muscle ache or pain	78	5.0	180	3.5	1.96 (0.74–5.18)	129	3.4	314	2.4	1.40 0.56–3.49)	94	3.6	205	2.3	2.57 0.65–10.14)	1.69 (0.79–3.59)
Fever	14	0.9	23	0.5	3.26 (0.81–13.10)	5	0.1	8	0.1	1.88 (0.42–8.40)	0	0	13	0.1	..	2.78 (0.93–8.34)

[a] *n* represents number of responses stating the presence of the specified symptom within the previous 24 h; % represents the proportion of all responses.

[b] Adjusted odds ratios with 95% confidence intervals (CI) were obtained from conditional logistic regression models with 1:3 matching of positive-test with negative-test participants for testing date (± 2 days) and sex (male, female). Models were adjusted for age (<30, 30–39, 40–49, 50–59, and ≥60 years), smoking (current, previous, and never), and occupation (nursing staff, medical doctors, biomedical laboratory scientists, medical secretaries, and other), except for analyses of reduced or lost sense of taste and smell, and fever, due to unstable estimates that did not provide valid confidence intervals by bootstrapping. Adjusted odds ratios for days 0–90 were furthermore adjusted by time since testing (days 0–30, 31–60, and 61–90). The conditional logistic regression models provided instantaneous odds ratios that could not be estimated from the period cumulative numbers and percentages in the table.

Table 3
Adjusted odds ratios for any symptom[a] by SARS-CoV-2 test result, age, sex, testing date, and time since testing.

	Time since the test															
	Day 0–30					Day 31–60					Day 61–90					Day 0–90
	Positive test and recording of any symptom[b]		Negative test and recording of any symptom[b]		Adjusted odds ratio (95% CI)[c]	Positive test and recording of any symptom[b]		Negative test and recording of any symptom[b]		Adjusted odds ratio (95% CI)[c]	Positive test and recording of any symptom[b]		Negative test and recording of any symptom[b]		Adjusted odds ratio (95% CI)[c]	Adjusted odds ratio (95% CI)[c]
	n	%	*n*	%		*n*	%	*n*	%		*n*	%	*n*	%		
Age																
<45 years	378	50.3	640	28.3	4.18 (2.20–7.97)	558	32.6	1340	22.3	2.17 (1.20–3.93)	301	27.8	727	17.4	1.96 (0.89–4.31)	2.43 (1.42–4.16)
≥45 years	484	60.4	786	27.8	4.33 (2.15–8.72)	1131	53.4	1264	18.3	5.04 (2.63–9.66)	702	46.0	592	12.3	8.50 (3.33–21.67)	5.37 (2.84–10.14)
p-Value[d]					0.95					0.08					0.02	0.07
Sex																
Female	782	56.8	1293	28.3	4.26 (2.60–6.98)	1569	47.5	2271	20.2	4.16 (2.73–6.36)	954	42.9	1098	14.6	5.51 (2.92–10.39)	4.38 (2.90–6.60)
Male	80	45.7	133	25.0	3.51 (0.87–14.8)	120	23.0	333	20.1	1.03 (0.31–3.48)	49	12.8	221	15.1	1.10 (0.03–40.0)	1.44 (0.48–4.36)
p-Value[d]					0.80					0.03					0.38	0.05
Testing date																
≤April 7, 2020	229	63.4	482	36.9	5.34 (2.47–11.54)	1070	48.6	1840	24.4	3.43 (2.14–5.48)	777	41.8	980	14.9	5.49 (2.74–11.00)	4.11 (2.51–6.74)
>April 7, 2020	633	53.1	944	24.9	3.90 (2.16–7.06)	619	38.1	764	14.2	3.83 (1.83–8.01)	226	30.3	339	14.0	2.79 (0.87–9.00)	3.59 (1.90–6.77)
p-Value[d]					0.55					0.79					0.30	0.73

[a] Any symptom includes reduced or lost sense of taste and smell, dyspnea, cough, headache, sore throat, muscle aches or pain, and fever.
[b] *n* represents number of responses stating the presence of any symptom within the previous 24 h; % represents the proportion of all responses.
[c] Adjusted odds ratios with 95% confidence intervals (CI) were obtained from conditional logistic regression models with 1:3 matching of positive–test with negative-test participants for testing date (± 2 days) and sex (male, female). Models included test result (positive, negative), age (<45 years, ≥45 years), smoking (current, previous, and never), occupation (nursing staff, medical doctors, biomedical laboratory scientists, medical secretaries, and other), and the interaction term between test result and age, test-result and sex, or test result and testing date (≤April 7, >April 7). Adjusted odds ratios for days 0–90 were furthermore adjusted by time since testing (days 0–30, 31–60, and 61–90). The conditional logistic regression models provided instantaneous odds ratios that could not be estimated from the period cumulative numbers and percentages of the table. Confidence intervals were obtained by bootstrapping.
[d] The *p*-value relates to the interaction term between test result and age, test result and sex, and test result and testing date.

After 30 days, no difference between the two test results was observed. At the time of the test, sore throat, muscle aches or pain, and fever were reported by 35%, 30%, and 20% of the positive-test participants, respectively, which was slightly more than among the negative-test participants. No differences were indicated for these symptoms after 30 days of follow-up.

Positive-test participants aged 45 years or older showed an overall five-fold increase in odds ratio (aOR 5.37, 95% CI 2.84–10.14) for any symptom compared with negative-test participants of the same age (Table 3). The corresponding odds ratio obtained among participants <45 years of age was 2.43 (95% CI 1.42–4.16) and the *p*-value of the interaction term was 0.07. Similar patterns were seen for days 31–60 and days 61–90, but not for days 0–30. When breaking this analysis down according to the seven symptoms, it appeared that this effect modification by age was primarily for reduced or lost sense of taste and smell, and headache, more than 30 days after the test (Supplementary Table S1).

Women who tested positive reported any symptom more often than women who tested negative (aOR 4.38, 95% CI 2.90–6.60), while this was not the case for men (aOR 1.44, 95% CI 0.48–4.36; Table 3); the *p*-value of the interaction term was 0.05. A similar pattern was seen for days 30–60 and days 61–90, but not for days 0–30. After day 30, much higher prevalences of reduced sense of taste and smell were seen for positive-test women relative to negative-test women than for positive-test men relative to negative-test men (Supplementary Table S2). A similar pattern was suggested for dyspnea, but at a lower level.

Early versus late testing date (≤April 7 vs >April 7) did not modify the association between a positive test and any symptom (Table 3).

Among study participants reporting any symptom the previous day, those who tested positive did not respond more often on the present-day questionnaire than those who tested negative (aOR 0.93, 95% CI 0.75–1.15; Table 4). This was also the case among participants reporting no symptoms the previous day (aOR 1.15, 95% CI 0.88–1.51). The *p*-value of the interaction term was 0.19, which indicated that responding to the questionnaire did not depend on the presence of symptoms the previous day and the test result.

Women, middle-aged employees, and nursing staff were more prevalent in the study population than in the source population (Supplementary Table S3).

Discussion

Key results

Nearly one-third of SARS-Cov-2 positive-test participants and close to zero of negative-test participants reported a reduced sense of taste and smell during all 90 days of follow-up. Dyspnea was reported by an initial 20% of positive-test participants and declined gradually to about 5% after 30 days without ever reaching the level of the negative-test participants. Cough, headache, sore throat, muscle aches, and fever were temporarily higher among the positive-test participants; however, after 30 days no increases were seen. Women tended to be more susceptible to reduced sense of taste and smell, and dyspnea, and participants aged 45 years or older to reduced sense of taste and smell, and headache, beyond 30 days.

Limitations and strengths

The major limitation of our study was the participants' awareness of their test results before reporting symptoms, which was expected to have inflated reporting among the positive-test participants. Such an effect was probably strongest for loss of sense of taste and smell, which had gained public awareness worldwide and nationally (DR [Danish Broadcasting Corporation], 2020; Mahase, 2020).

Another limitation was that there were only a few observations during the first weeks after testing. Thus, the study primarily addressed the course of symptoms after the initial acute phase of infection.

The prospective design, with daily collection of symptom reports that provided information with high temporal resolution, was a major strength and allowed us to record the courses of symptoms day by day. Another strength was the inclusion of a reference group of negative-test participants recruited within the same population as the positive-test healthcare workers, and tested with the same kit at the same time. This allowed us to take symptoms among the positive-test participants that were not attributed to SARS-CoV-2 infection into consideration, and also to account for rapid changes in indications for testing, infection rates, and testing rates in the population. Matching for sex and adjusting for age, smoking, and occupation was designed to have further reduced potential confounding.

Our access to the results of all SARS-CoV-2 tests conducted by the Health Authorities on all samples obtained in the Central Denmark Region during the study period, independently of the participants, should have ensured inclusion of all tested participants and precluded selection or information bias relating to testing status. One-third of the invited employees volunteered for symptom reporting and, among these, one third of participants were PCR tested. Relatively more nursing staff participated in the study compared with other occupations with limited patient contact. This would have increased the proportion of positive-test participants, but should not have affected the validity of symptom comparisons between positive-test and negative-test participants (Jespersen et al., 2020).

Indication for a SARS-CoV-2 PCR test, as well as testing and infection rates, changed during the course of the study. For this

Table 4
Odds ratios for responding on the present-day questionnaire by any symptoms the previous day and SARS-CoV-2 PCR test result.

Any symptom on the previous day[a]					No symptom on the previous day					
Positive test[b]		Negative test[b]		Adjusted odds ratio (95% CI)[c]	Positive test[b]		Negative test[b]		Adjusted odds ratio (95% CI)[c]	*p*-Value[d]
N	%	*n*	%		*n*	%	*n*	%		
3001	85.5	4485	84.5	0.93 (0.75–1.15)	3683	84.5	17 870	84.0	1.15 (0.88–1.51)	0.19

[a] Any symptom includes reduced or lost sense of taste and smell, dyspnea, cough, headache, sore throat, muscle aches or pain, and fever.
[b] *n* represents number of responses stating the presence of any symptom within the last 24 h and % represents the proportion of all responses.
[c] Odds ratios with 95% confidence intervals (CI) were obtained from conditional logistic regression models with 1:3 matching for positive-test with negative-test participants on testing date (± 2 days) and sex (male, female). Models included test result (positive, negative), age (<30, 30–39, 40–49, 50–59, and ≥60 years), smoking (current, previous, and never), occupation (nursing staff, medical doctors, biomedical laboratory scientists, medical secretaries, and other), time since testing (days 0–30, 31–60, and 61–90), and the interaction term between any symptom the previous day and the test result. The conditional logistic regression model provided instantaneous odds ratios that could not be estimated from the cumulative numbers and percentages of the table. Confidence intervals were obtained by bootstrapping.
[d] The *p*-value relates to the interaction term between any symptom the previous day and the test result.

reason, participants were matched individually according to testing date. No difference was observed in the association between test result and any symptom among participants tested early versus those tested late during spring 2020, indicating that matching had fulfilled its purpose. No indications were observed that responding to the questionnaire on a given day depended on test results and symptoms the previous day, which indicated no differential attrition.

Comparisons with other studies

Our finding of a highly and constantly increased prevalence of reduced or lost sense of taste and smell among the SARS-CoV-2 positive-test participants compared with the negative-test participants was partly in accordance with two recent reports involving general population samples in Israel and the USA, including few or no participants hospitalized for COVID-19 (Cirulli et al., 2020). Both studies showed initial prevalences among the positive-test participants comparable with ours, but these declined to about 5% after 20 days and to 14% after 90 days, respectively. In both studies, symptom prevalences of lost sense of taste and smell among negative-test participants were constantly close to zero during follow-up, in line with our findings. High initial prevalences of altered sense of smell and taste of 60–90% followed by steep recovery rates of 41–87% during 30 days of follow-up have been reported in non-hospitalized patient series (Boscolo-Rizzo et al., 2020; Paderno et al., 2020). Similar findings were also seen in a follow-up study of mainly COVID-19 outpatients examined using olfactory and gustatory psychophysical tests (Vaira et al., 2020). During the first few days after the test, 85% had taste and smell dysfunction, which gradually declined to 7% 60 days later.

A five-fold increase in prevalence of dyspnea among positive-test participants compared with negative-test participants (16% vs 3%) 90 days after testing has been reported, which was in line with our findings but at a higher absolute level (Cirulli et al., 2020; Mizrahi et al., 2020). Others have reported a constant level of dyspnea of 30% among positive-test participants during 14–21 days of follow-up in a study that included no reference group, as well as minor differences between positive-test and negative-test participants during 20 days of follow-up (Mizrahi et al., 2020; Tenforde et al., 2020).

Increased prevalences of cough, sore throat, body aches, and fever among positive-test relative to negative-test individuals 90 days after testing (Cirulli et al., 2020), high prevalences of the same symptoms among positive-test individuals 14–21 days after testing (Tenforde et al., 2020), as well as no relative symptom increase in positive-test individuals 20 days after testing, have been reported (Statens Serum Institut, 2020b); the latter finding being in line with ours. It should be stressed that our study accounted for testing date, and this may explain some of the inconsistencies between earlier findings and ours (Cirulli et al., 2020; Mizrahi et al., 2020).

Our data suggest that women and older individuals are more susceptible than men and younger individuals to suffering from long-lasting COVID-19-related symptoms. There is ample evidence of men being more severely affected by COVID-19 than women, and our contradictory findings may point towards explanations other than SARS-CoV-2 infection per se (Scully et al., 2020).

Conclusion

Our study observed a highly increased prevalence of long-lasting reduced or lost sense of taste and smell among participants diagnosed with mild COVID-19. This pattern was also seen for dyspnea at a low level but not for cough, sore throat, headache, muscle ache or pain, or fever. Women and participants aged 45 years or older tended to be more susceptible to long-lasting SARS-CoV-2 symptoms.

Ethical approval

This study was approved by the Danish Data Protection Agency (Jnr 1-16-02-150-20) and the Danish Patient Safety Authority (Jnr 1-45-70-25-20). The Regional Scientific Ethics Committee of the Central Denmark Region concluded that this study did not require scientific ethical approval (Jnr 1-10-72-1-20).

Data availability

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

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Author contributions

HAK, KJN, JMV, VS, KB, OC, KKH, AD, MLH, ETW, and TG planned the study and collected the data. TG and MKT were responsible for PCR tests. HAK, JMV, KJN, VS, JPB, KAK, and KHK analyzed the data. HAK, JMV and KJN drafted the manuscript. KJN, AD, KB, ETW, KAK, KKH, and HAK performed the literature search. JMV designed the figures. All authors interpreted and critically revised the manuscript, and approved the final version. HAK, KJN, and JMV verified the underlying data.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2021.05.032.

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