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MAJOR ARTICLE

Persistent Symptoms and Sequelae After Severe Acute Respiratory Syndrome Coronavirus 2 Infection Not Requiring Hospitalization: Results From Testing Denmark, a Danish Cross-sectional Survey

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Background. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with persistent symptoms ("long COVID"). We assessed the burden of long COVID among nonhospitalized adults with polymerase chain reaction (PCR)–confirmed SARS-CoV-2 infection.

Methods. In the fall of 2020, a cross-sectional survey was performed in the adult Danish general population. This included a self-administered point-of-care test for SARS-CoV-2 antibodies, the Short Form Health Survey (SF-12), and coronavirus disease 2019 (COVID-19)–associated symptom questions. Nonhospitalized respondents with a positive SARS-CoV-2 PCR test ≥12 weeks before the survey (cases) were matched (1:10) to seronegative controls on age, sex, and body mass index. Propensity score–weighted odds ratios (ORs) and ORs for risk factors were estimated for each health outcome.

Results. In total, 742 cases and 7420 controls were included. The attributable risk of at least 1 long-COVID symptom was 25.0 per 100 cases (95% confidence interval [CI], 22.2–27.4). Compared to controls, cases reported worse general health (OR, 5.9 [95% CI, 5.0–7.0]) and had higher odds for a broad range of symptoms, particularly loss of taste (OR, 11.8 [95% CI, 9.5–14.6]) and smell (OR, 11.2 [95% CI, 9.1–13.9]). Physical and Mental Component Summary scores were also significantly reduced with differences of −2.5 (95% CI, −3.1 to −1.8) and −2.0 (95% CI, −2.7 to −1.2), respectively. Female sex and severity of initial infection were major risk factors for long COVID.

Conclusions. Nonhospitalized SARS-CoV-2 PCR–positive individuals had significantly reduced physical and mental health, and 1 in 4 reported persistence of at least 1 long-COVID symptom.

Keywords. COVID-19; cross-sectional study; health-related quality-of-life; long COVID; nonhospitalized patients.

In the early phases of the coronavirus disease 2019 (COVID-19) pandemic, it became evident that patients recovering from COVID-19 hospitalization often experienced persistent symptoms including fatigue, shortness of breath, and loss of smell and taste [1–3]. These health effects also affect those with mild or asymptomatic infection [4–6]. Estimates of persistence of at least 1 symptom vary widely with prevalence up to 73% in certain populations [7, 8]. The syndrome has been called long COVID, persistent COVID, post-COVID syndrome or condition, or postacute sequelae of severe acute

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respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Since October 2021, the World Health Organization defines long COVID as a condition present 3 months after probable or confirmed SARS-CoV-2 infection, with symptoms for at least 2 months and without other probable causes [9].

Studies to characterize long COVID and assess its prevalence have focused on patients discharged from hospital after COVID-19, including large-scale register-based studies and prospective cohort studies [10–18]. These studies showed a diverse picture of long COVID, but insight into long-COVID symptoms, risk factors, and quality of life among the nonhospitalized population with polymerase chain reaction (PCR)–confirmed SARS-CoV-2 infection compared to seronegative controls is still urgently needed to evaluate the long-term health consequences of the pandemic.

In the fall of 2020, a nationwide cross-sectional survey study, "Testing Denmark," was carried out, with >300 000 responses including an at-home point-of-care test for SARS-CoV-2 antibodies [19]. Here we investigated the occurrence and risk factors for long-COVID symptoms and health-related quality of life among PCR-confirmed nonhospitalized respondents infected during spring and summer 2020, comparing them to seronegative controls from the general population.

METHODS

Study Design and Data Sources

"Testing Denmark" was a cross-sectional serological survey in the Danish population in September and October 2020. The survey contained 2 parts: (1) a questionnaire and (2) an at-home self-administered antibody point-of-care test (POCT). The study outline and results of the POCT were reported previously [19]. In short, 1.3 million residents, aged >15 years, were randomly identified from the Danish Civil Registration System and invited to participate between 25 September and 7 October 2020. The first approximately 420 000 responders were offered an immunoglobulin G (IgG) and immunoglobulin M (IgM) antibody POCT kit sent to their home address (Livzon Diagnostics, Zhuhai, Guangdong, China). Respondents self-report the results of the POCT. Questionnaires were administered using Enalyzer software (Enalyzer, Copenhagen, Denmark), a secure web-based questionnaire tool.

Previously registered positive PCR tests were obtained from the National Surveillance System for COVID-19, which contains all SARS-CoV-2–positive PCR tests performed in Denmark linked to personal identification numbers. Negative test results were not available. Information on COVID-19–associated hospitalization and underlying comorbidities were obtained from the Danish National Patient Register.

Questionnaire and Outcome Measures

The questionnaire contained questions on the respondent's self-rated change in the last year in general, physical, and mental health; pain, mood, and weight; and COVID-19–related symptoms (loss of sense of taste and smell; shortness of breath during rest, talk, and easy and fast walk; tiredness; concentration problems; screen fatigue; long- and short-term memory problems; tightness in the chest; dry cough; headache; muscle pain; dizziness; light and noise sensitivity; nausea; diarrhea; vomiting; constipation; and tingling feelings in hand and feet). All questions were rated on a 5-point scale from "much worse" to "much better." Respondents who thought to have been infected with SARS-CoV-2 were asked how they felt when their "perceived" initial infection was at its worst: "asymptomatic," "symptomatic at home," "bedridden at home," "hospitalized," or "hospitalized and on respirator." We used these responses as a proxy for severity of initial infection. Health-related quality of life was measured with the 12-Item Short-Form Health Survey version 1 (SF-12), which summarizes health-related quality of life into Physical and Mental Component summary scores (PCS and MCS, respectively) [20]. These scores are on a scale of 0–100 points, where higher scores relate to better health, and each question contributes differently to both scores [21]. The outcome measures for this study were self-reported changes in health, long COVID–related symptoms, and PCS and MCS scores.

Study Populations

Respondents with a positive SARS-CoV-2 PCR test at least 12 weeks before the date of answering the questionnaire were included as cases [9]. We defined controls as respondents with negative POCT and no known positive PCR test. When a control's IgG and IgM POCT had both failed, were inconclusive, or were absent, they were excluded from the study, as were all respondents who either self-reported or were registered to have been hospitalized with COVID-19 (Figure 1). Cases were matched 1:10 to controls on age, sex, and body mass index (BMI) using greedy nearest neighbor method without replacement.

Statistical Analysis

Adjusted odds ratios (ORs) comparing cases to controls for each long COVID–related symptom or change in health, regardless of severity, were estimated using generalized linear models with binomial distribution and log link. Attributable risks were estimated as the proportional differences between cases and controls. ORs were adjusted for confounding by propensity score weighting with robust 95% confidence intervals (CIs). Propensity scores were set to 1 for cases, and controls were weighted according to the propensity score odds to have a positive PCR test [22]. The propensity score model included the following covariates: smoking status (nonsmoker vs smoker), alcohol consumption (nondrinker, <1 unit per week, 2–6 units per week, or ≥7 units per week), BMI (normal weight, overweight [BMI >25 kg/m^2], and obesity [BMI >30 kg/m^2]),

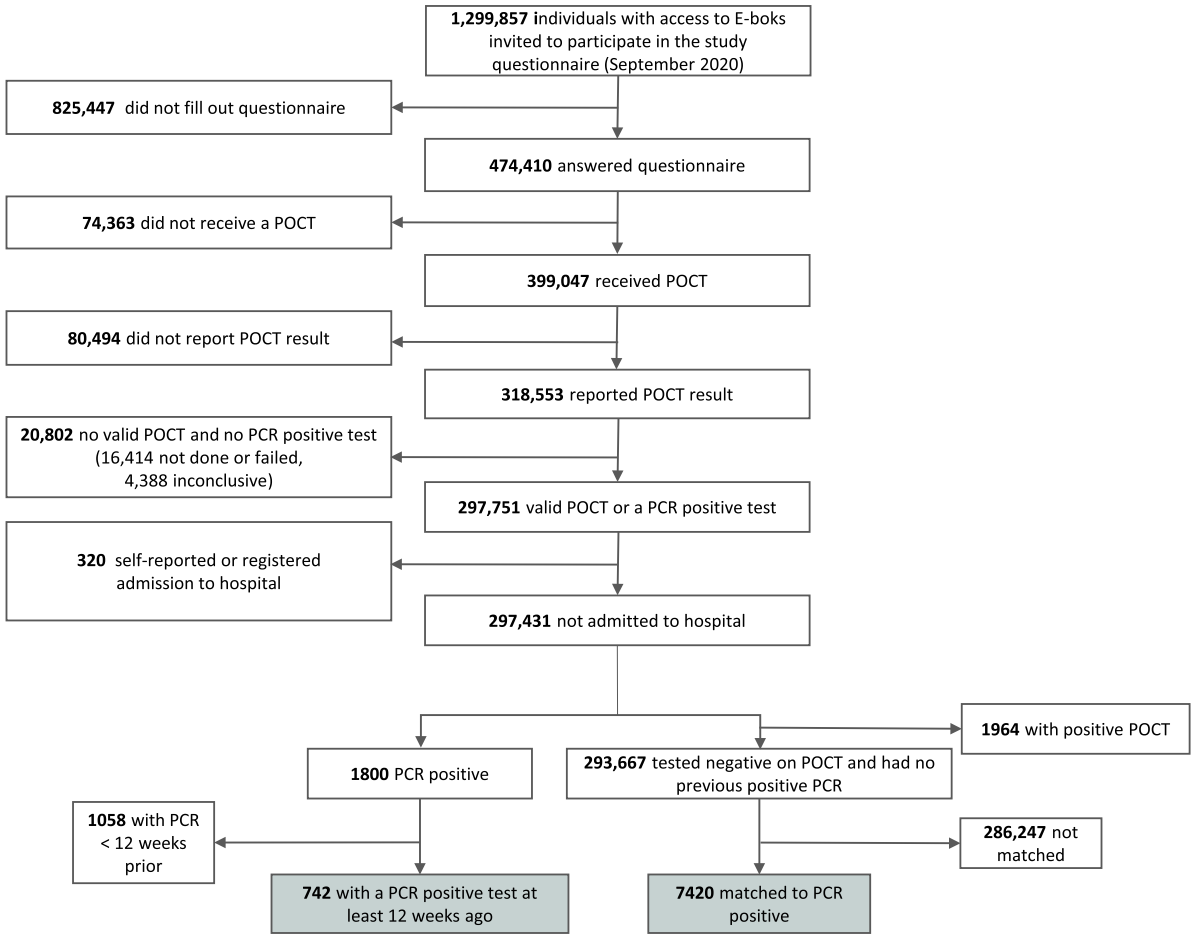

Figure 1. Flow-diagram of study population selection. Gray boxes indicate study populations used in the statistical analyses. Abbreviations: E-boks, a secure personal electronic mail box; PCR, polymerase chain reaction; POCT, point-of-care test.

comorbidities (asthma or other respiratory conditions, diabetes, cardiovascular disease including blood clots and hypertension, and prior or current cancer), and occupation (healthcare worker or not). Covariate balance was checked with standardized mean differences and a difference of <0.1 was considered insignificant [23].

To assess the impact of severe initial infection, we also restricted the above analysis to mild or asymptomatic initial infections. Similarly, knowledge of a previous positive PCR test may affect respondents' answers. We therefore re-matched cases to a subset of controls who believed they had been infected before. Furthermore, to investigate the influence of COVID-19–related symptoms on associations between case or control status and worsening of general, physical, and mental health, we performed mediation analyses for each symptom separately. For each symptom, 2 models were constructed: 1 with the symptom as the dependent variable and case/control status as the independent variable, and another with general, physical, or mental health as the dependent variable and case/control status as well as the mediating symptom included as independent variables. Each model was furthermore adjusted for age group (15–29, 30–39, 40–49, 50–59, ≥60), sex (male or female), BMI, smoking status, alcohol consumption, whether the respondent received the 2019–2020 influenza season vaccine, and comorbidities (including diabetes, cardiovascular disease, asthma or other respiratory conditions, cancer, and other comorbidities). The analysis was performed using the Mediation package in R with CI base on robust standard errors.

Risk factors for long-COVID symptoms were assessed among cases using multivariable logistic regressions for each symptom separately. We included the following covariates: sex, age group (as above), BMI, smoking status, alcohol consumption, received 2019–2020 influenza season vaccine, initial COVID-19 symptoms (asymptomatic, symptomatic at home, bedridden at home), time since positive PCR test (12–24 weeks, ≥25 weeks), and comorbidities (as above).

We calculated PCS and MCS scores and imputed missing weights (see Supplementary Appendix and Supplementary Figure 1) [21, 24, 25]. We compared PCS and MCS scores between cases and controls with propensity score–weighted

generalized multivariate linear models with Gaussian link and robust 95% CIs, and assessed associations using interaction terms for each covariate separately, adjusting for all other covariates (as above). Statistical significance of interaction terms was tested using F-tests. Only cases and their matched controls without missing values for PCS and MCS were used for this analysis.

All analyses were done in R version 4.1.1 (R Foundation, www.r-project.org).

Data Sharing Statement

Data were collected for the purpose of the Testing Denmark study only and cannot be shared due to data protection regulations. Part of the data may however, be made available in a de-identified format for access to members of the scientific and medical community for noncommercial use only, by contacting the authors.

RESULTS

In total, 1 299 857 individuals were invited to participate in the study and 474 410 (36.5%) answered the questionnaire. Of 399 047 who received a POCT kit, 297 751 (74.6%) reported valid results or had a positive PCR test, and of these 297 431 were nonhospitalized. There were 742 with a positive PCR test at least 12 weeks before the survey and 293 667 seronegative respondents, of whom 7420 were matched to cases (Figure 1). In total 49.6% of PCR-positive tests were taken 24 weeks or more before the questionnaire (Supplementary Figure 2).

There were fewer smokers among cases than matched controls and more healthcare workers, and more had a respiratory condition. Among cases, 64.4% reported having been bedridden at home during their initial COVID-19 infection. After matching and propensity score weighting, satisfactory balance was achieved for all covariates (Table 1, Supplementary Figure 3; see Supplementary Table 1 for characteristics by severity of initial infection).

Long COVID–Related Symptoms and Health Impact

Considerably more cases reported a worsening of health, with overall health rated worse in 48.5% of cases, compared to 13.8% of controls (difference: 34.8% [95% CI, 31.6%–38.4%]; Figure 2). Similarly, physical and mental health and mood had declined more often, and cases more often reported increased pain.

The overall burden of at least 1 long-COVID symptom was 62.5 per 100 controls and 87.5 per 100 cases—an attributable risk of 25.0 per 100 cases (95% CI, 22.2–27.4). This increased with increasing severity of initial infection, being 6.8 (95% CI, −5.3 to 16.7), 19.9 (95% CI, 13.9–24.7), and 29.6 (95% CI, 26.5–32.0) per 100 asymptomatic, symptomatic, and bedridden at home cases, respectively. See also Supplementary Figure 4. Cases more often than controls reported worsening of symptoms for loss of sense of taste and smell; shortness of breath during rest, talk, and easy and fast walk; tiredness; concentration problems; screen fatigue; long- and short-term memory problems; tightness in the chest; dry cough; headache; muscle pain; dizziness; light and noise sensitivity; nausea; diarrhea; and tingling feelings in hands and feet (Supplementary Table 2). The respondents' answers by severity are presented in Supplementary Figures 5 and 6.

After propensity score weighing, the highest ORs were found for loss of sense of taste and smell (OR, 11.8 [95% CI, 9.5–14.6] and 11.2 [95% CI, 9.1–13.9]), respectively, followed by reduced general health with an OR of 5.9 (95% CI, 5.0–7.0). A similar pattern was seen when restricting to mild or asymptomatic initial infection, although the ORs were generally lower (Supplementary Figure 9). When matching to controls who thought to have been infected, all OR were considerably lower, but strong associations remained for declined general, physical, and mental health, as well as increased risks for loss of sense of taste and smell, shortness of breath, tiredness, and concentration problems (Supplementary Table 8, Supplementary Figures 10–12). In this analysis, the burden of at least 1 symptom was 6.2 (95% CI, 3.5–8.6) per 100.

As impaired general health was an important outcome, we further investigated the mediating role of each COVID-19–related symptom on the association between a positive PCR test 12 or more weeks prior and worsening of general health. We did the same for physical and mental health (Figure 3 and Supplementary Tables 9–11). Tiredness, shortness of breath during an easy or fast walk, concentration problems, and loss of sense of smell and taste were all important mediators, each explaining >25% of the estimated association. For general health, tiredness explained 46% (95% CI, 41%–51%) of the association for cases and 28% (95% CI, 24%–32%) for controls. For physical and especially mental health, these symptoms explained a larger proportion of the association. For example, tiredness explained 50% (95% CI, 44%–56%) and 36% (95% CI, 31%–41%) of the association between PCR positivity and physical health for cases and controls, respectively, and 87% (95% CI, 72%–109%) and 82% (95% CI, 64%–112%) for mental health, respectively.

Long COVID Risk Factors

Next, we investigated risk factors associated with long-COVID symptoms among cases (Figure 4 and Supplementary Tables 3–5). Female sex or being bedridden during initial infection were the major risk factors for long-COVID symptoms; the latter leading to high ORs for reduced general health (OR, 7.3 [95% CI, 3.5–15.2]), physical health (5.3 [95% CI, 2.6–10.7]), and shortness of breath during rest (5.3 [95% CI, 1.6–18.2]), fast walk (5.4 [95% CI, 2.8–10.4]), and easy walk (5.3 [95% CI, 2.3–12.4]).

Other risk factors were associated with a fewer symptoms. Decreased general and physical health was more likely in those

Table 1. Characteristics of the Study Population Before and After Matching

Characteristic	Cases (N = 742)	Controls, Before Matching (n = 293 667)	Matched Controls (n = 7420)	Standardized Mean Difference, Weighted[a]
Age, y, mean (SD)	48.2 (15.0)	50.7 (16.4)	48.2 (15.0)	<0.01
Age group, y				
15–29	117 (15.8)	40 507 (13.8)	1173 (15.8)	
30–39	100 (13.5)	36 450 (12.4)	999 (13.5)	
40–49	137 (18.5)	52 825 (18.0)	1371 (18.5)	
50–59	196 (26.4)	66 180 (22.5)	1957 (26.4)	
≥60	192 (25.9)	97 705 (33.3)	1920 (25.9)	
Male sex	245 (33)	124 171 (42.3)	2450 (33)	<0.01
BMI, kg/m^2, mean (SD)	26.5 (5.6)	26.3 (5.2)	26.5 (5.6)	0.01
Normal	368 (49.6)	135 344 (46.1)	3680 (49.6)	
Overweight	226 (30.5)	102 561 (34.9)	2250 (30.4)	
Obese	148 (19.9)	55 762 (19.0)	1488 (20.1)	
Smoking				<0.01
Nonsmoker	633 (85.3)	239 912 (81.7)	5983 (80.6)	
Current smoker	109 (14.7)	53 755 (18.3)	1437 (19.4)	
Alcohol, units/week				<0.01
Nondrinker	92 (12.4)	28 765 (9.8)	741 (10.0)	
≤1	235 (31.7)	86 650 (29.5)	2415 (32.5)	
2–6	260 (35.0)	109 710 (37.4)	2758 (37.2)	
≥7	155 (20.9)	68 542 (23.3)	1506 (20.3)	
Healthcare occupation	279 (37.6)	26 598 (9.1)	806 (10.9)	<0.01
Influenza vaccine 2019–2020	165 (22.2)	67 754 (23.1)	1382 (18.6)	0.05
Comorbidities[b]				
Asthma or other respiratory condition	158 (21.3)	48 716 (16.6)	1225 (16.5)	<0.01
Diabetes	46 (6.2)	16 412 (5.6)	352 (4.8)	<0.01
Cancer	56 (7.5)	21 314 (7.3)	418 (5.6)	<0.01
Cardiovascular disease	187 (25.2)	80 402 (27.4)	1759 (23.7)	<0.01
Other comorbidity[c]	409 (55.1)	143 062 (48.7)	3751 (50.6)	<0.01
Severity of initial infection[d]				3.11
Asymptomatic	65 (8.8)	273 283 (93.1)	6879 (92.7)	
Symptomatic at home	199 (26.8)	6142 (2.1)	165 (2.2)	
Bedridden at home	478 (64.4)	14 242 (4.8)	376 (5.1)	

Data are presented as No. (%) unless otherwise indicated. Nonhospitalized cases with a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR)–positive test at least 12 weeks prior to answering the questionnaire were matched to seronegative respondents with no known positive PCR test. Matching was done on age, sex, and BMI using greedy nearest neighbor method without replacement.

Abbreviations: BMI, body mass index; SD, standard deviation.

[a]Standardized mean difference between cases and matched controls after propensity score weighting.

[b]Comorbidities for those without a PCR result are based only on self-reported comorbidities. For those with PCR results, this is supplemented with information from their hospital records.

[c]Other comorbidities include chronic neurological, kidney, and hematological complications, as well as rheumatoid arthritis, allergy, and other unspecified chronic conditions.

[d]Severity of initial infection is based on self-reported presumed previous infection with SARS-CoV-2. Numbers for controls indicate those who think to have been infected, and how they rate the infection when it was at its worst, but who do not have a known positive PCR test and are seronegative.

aged >40 years compared to 15- to 29-year-olds. Alcohol consumption was associated with a decreased odds of long COVID, while smoking increased the risk for declined general, physical, and mental health as well as several long COVID symptoms. Among comorbidities, only cardiovascular disease was a main risk factor, while current or previous cancer lowered the odds for dizziness symptoms. Time since positive PCR test was not a relevant risk factor.

Health-Related Quality of Life (SF-12)

Cases had lower, although similar, PCS and MCS compared to controls, with a median PCS score for cases of 54.1 (interquartile range [IQR], 46.0–57.6) compared to 56.3 (IQR, 51.4–57.9) for controls, and a median MCS of 49.5 (IQR, 41.3–55.0) for cases and 51.7 (IQR, 44.8–55.9) for controls. The adjusted differences were −2.5 (95% CI, −3.1 to −1.8; $P < 0.001$) and −2.0 (95% CI, −2.7 to −1.2; $P < 0.001$) for PCS and MCS scores, respectively (Supplementary Figure 8).

Risk factors for worsened PCS were as follows: increased age, female sex, obesity, smoking, and severity of initial infection (Supplementary Table 6). For MCS, the strongest risk factors were female sex, cardiovascular disease, and severity of initial infection (Supplementary Table 7). Overall, MCS did not differ in effect between cases and controls, while for PCS there were increased negative effects for cases of age and female sex, and positive effects of alcohol consumption.

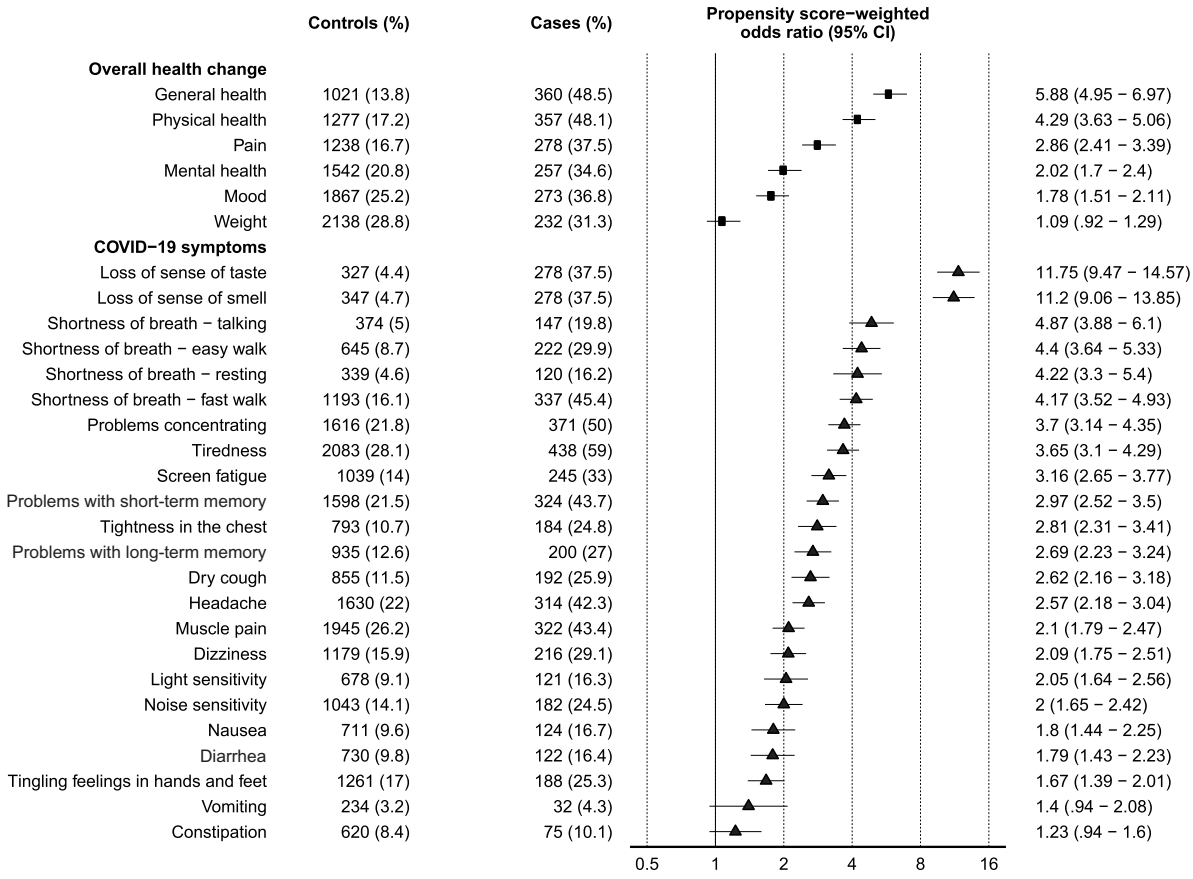

Figure 2. Odds ratios for self-reported declined health state in nonhospitalized respondents. Cases with a severe acute respiratory syndrome coronavirus 2 polymerase chain reaction (PCR)–positive test at least 12 weeks prior to answering the questionnaire were compared to matched and propensity score–weighted seronegative controls with no known positive PCR test, using generalized linear methods with robust confidence intervals. Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019.

DISCUSSION

Long COVID–related symptoms were common among nonhospitalized individuals after infection with SARS-CoV-2 during the first pandemic wave of 2020 in Denmark. General, physical, and mental health were all considerably reduced.

We estimated the burden of at least 1 long-COVID symptom 12 or more weeks after infection at 25.0 (95% CI, 22.2–27.4) per 100 nonhospitalized individuals—considerably more than previous estimates in the range of 7–14 per 100 [12, 13]. This difference might be explained by the cross-sectional design of our study, its serological test component, and using self-reported symptoms rather than information from health registries. A Norwegian study among nonhospitalized individuals found that 36% of cases and 18% of controls assessed their health as worse compared to the previous year [16]. Our study was done later in the pandemic, when awareness of long COVID was more widespread. Nonetheless, we found similar differences. In agreement with other studies, we also found that severity of initial infection and female sex were strongly related to long-COVID symptoms, but asthma and other respiratory conditions was only a risk factor for worsening of shortness of breath but not for other long-COVID symptoms [4, 6, 12, 14, 15, 26]. Similarly, diabetes was only associated with nausea, and cancer with decreased odds for dizziness and headache whereas cardiovascular disease increased risk for several symptoms [26]. Some of these associations might be explained by lockdowns exacerbating preexisting conditions. Interestingly, alcohol consumption decreased the risk of long-COVID symptoms—this may represent reverse causality: those with more symptoms were possibly less likely to have excess alcohol intake.

Comparing COVID-19 to influenza, Taquet et al found that 37% had at least 1 symptom 90 days after SARS-CoV-2 infection, compared to 30% for influenza [11]. They also found that cognitive symptoms were common. We unfortunately did not have access to information on other respiratory conditions, and while our controls come from the general population, we lacked baseline measures of potential mental health problems. However, we did find a worsening of mental health in 20.8% of the matched controls versus 34.6% among cases,

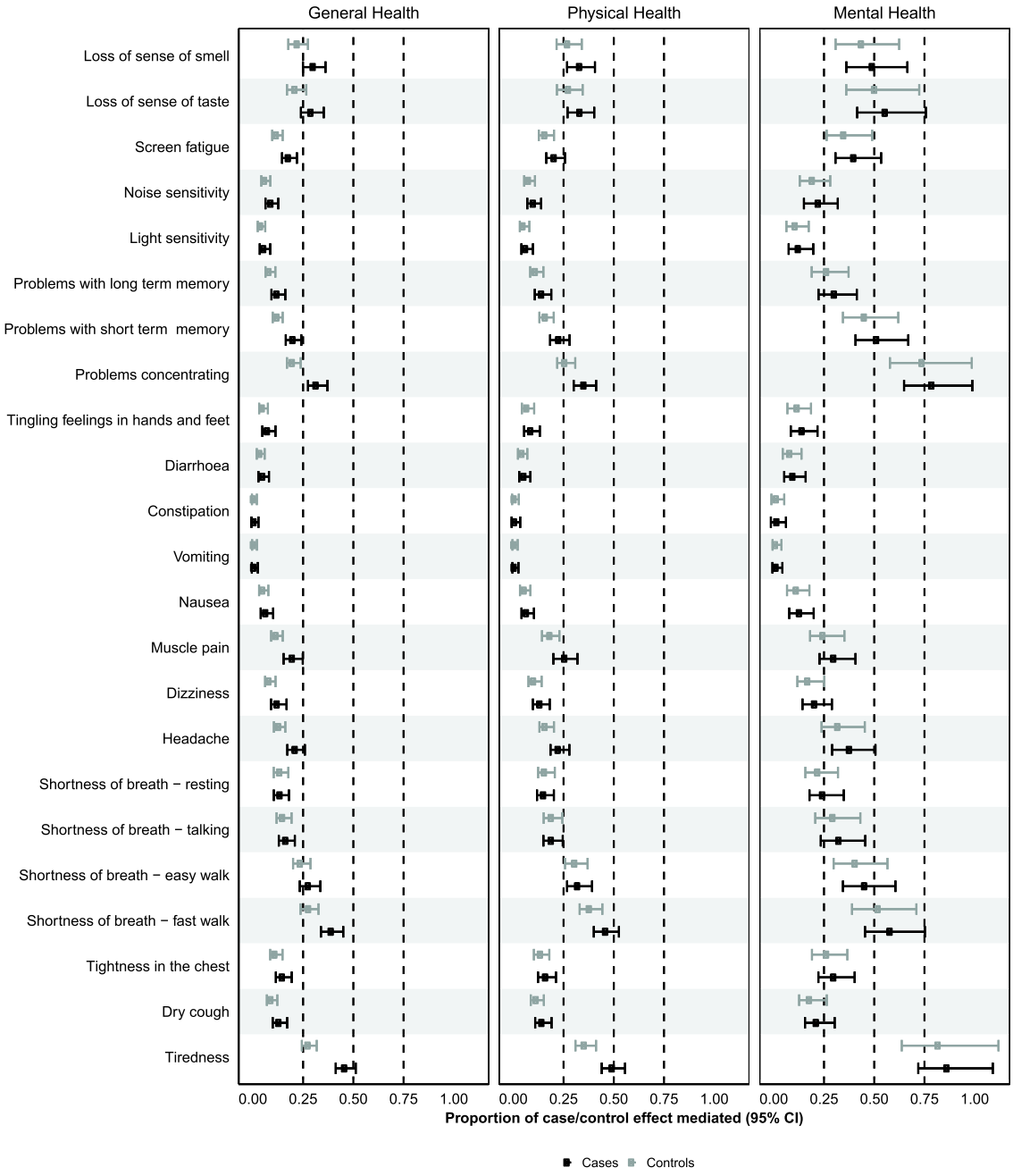

Figure 3. Mediation effect of long-COVID symptoms on general, physical, and mental health. Plots show the proportion of the effect of severe acute respiratory syndrome coronavirus 2–positive tests on general, physical, and mental health mediated through long COVID–related symptoms. Details can be found in Supplementary Tables 9–11. Abbreviation: CI, confidence interval.

and significantly higher risk for worsened concentration and short- and long-term memory. This further stresses the multifaceted nature of long COVID that goes well beyond the physical health symptoms [6, 12].

Contrary to our study, a Danish cohort study found a low risk for severe complications after SARS-CoV-2 infection [10]. In their study, Lund et al focused on complications requiring prescription medication or hospital visits, but they did find an increase in general practitioner visits. Our study was based on self-reported symptoms in nonhospitalized individuals. Together, this suggests that long-COVID symptoms may not be severe enough to seek medical attention in the hospital, but sufficiently disruptive to affect quality of life. Previous studies on health-related quality of life during the COVID-19 pandemic found that SARS-CoV-2 infection reduced overall quality of life [17, 27, 28]. While these studies primarily

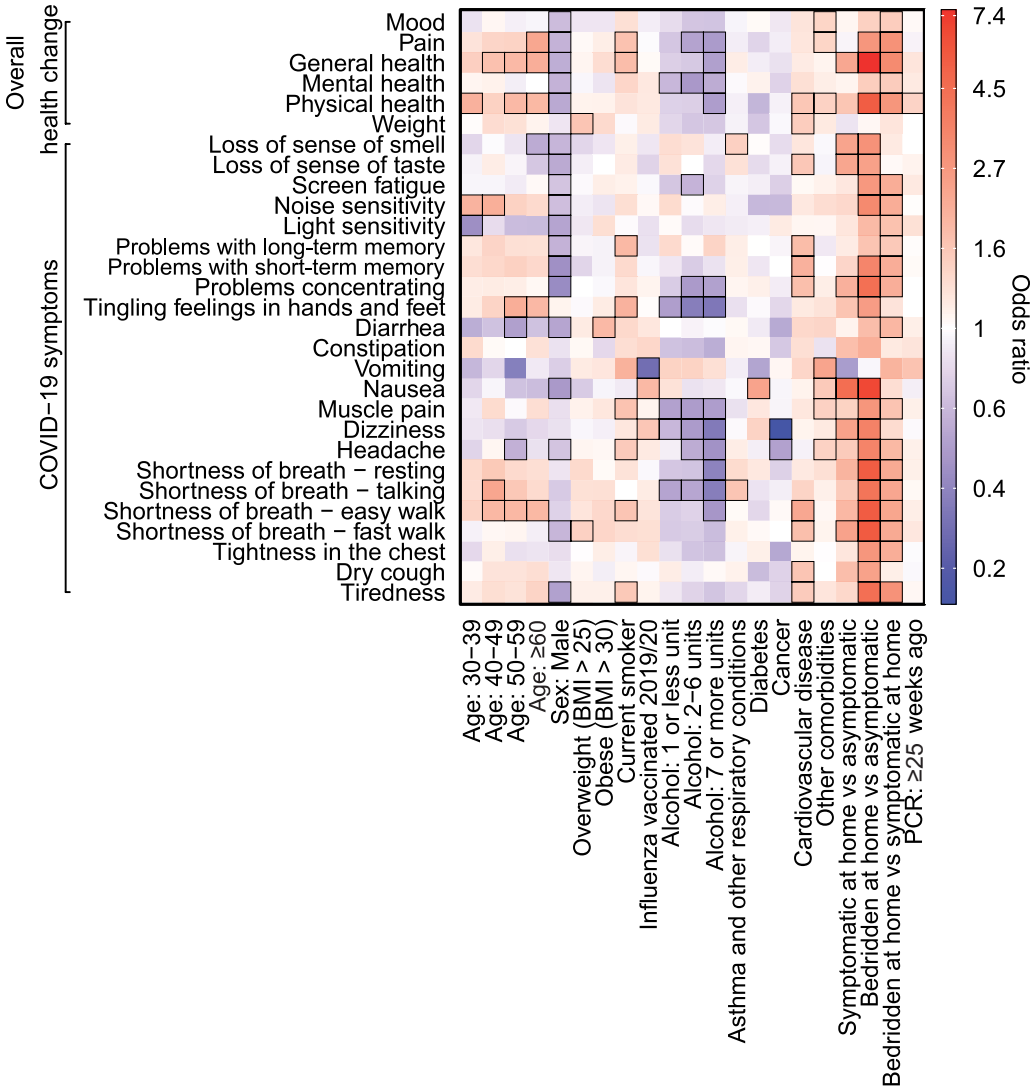

Figure 4. Odds ratios (ORs) for potential risk factors for changes in overall health and specific coronavirus disease 2019 (COVID-19)–related symptoms among nonhospitalized respondents with a severe acute respiratory syndrome coronavirus 2 polymerase chain reaction (PCR)–positive test at least 12 weeks before answering the questionnaire. ORs are multivariate adjusted; univariate ORs are presented in Supplementary Figure 7. ORs statistically significantly different from zero (at $\alpha = .05$) are indicated by solid lines around the cells. Confidence intervals are presented in Supplementary Tables 3–5. Reference groups: sex: female; age: 15–29 years; body mass index (BMI): normal weight; alcohol: nondrinker; smoking: nonsmoker or previous smoker; influenza vaccine: not vaccinated in 2019–2020; for comorbidities: no such condition; COVID-19: asymptomatic infection; PCR: 12–24 weeks ago.

included hospitalized patients and used SF-36 or EQ-5D questionnaires, we found similar results using the SF-12. Comparing our results to a Danish reference population from before the COVID-19 pandemic, we note that controls had similar median PCS score (56.3 vs a reference of 55.9), while cases had scored lower with 54.1 [24]. MCS scores were, however, lower for both cases and controls at 51.9 and 49.5, respectively, versus 54.4 in the reference. This suggests that SARS-CoV-2 infection particularly affected physical and mental health, while the pandemic primarily affected mental health in the general population. While the SF-12 results indicated small differences between cases and controls, cases reported considerably more often worsening in general health (48.5% vs 13.8%). Timing of the questions might explain part of the difference: The SF-12 questionnaire relates to the previous couple of weeks, whereas the question on general health-related changes refers to the year prior, that is, before the pandemic. Post hoc mediation analysis indicated that the higher risks for any COVID-19–related symptom, in particular tiredness, explained a large part of the worsened general, physical, and mental health among cases (Figure 3).

There are limitations to our study. First, the response rate to the questionnaire was 36.5%. It is likely that respondents with prior interest in the topic are more prone to respond, especially

PCR-positive respondents and those with COVID-19–related symptoms. In addition, at the time of the survey in October 2020, cases consisted of individuals with a positive PCR test for SARS-CoV-2 taken early on in the pandemic when access to PCR tests was restricted and primarily available to those with more severe symptoms or performing critical functions, such as hospital staff. About 50% of PCR tests were taken between February and mid-April 2020. This explains the overrepresentation of people bedridden at home during initial infection and the high proportion of healthcare personnel among cases. Together, these factors may have biased our results to a subpopulation of more severely infected individuals, and potentially more severe long-COVID symptoms. In extension, our results only pertain to the variants related to the ancestral Wuhan SARS-CoV-2 strain, which were dominant in Denmark until January 2021.

Second, this study was based on self-reported symptoms, and only for those with a positive PCR test was additional information on comorbidities available from health registers. We thus had more accurate and complete information on comorbidities for cases. The matched design with propensity score weighting adjusted partially for this bias. Furthermore, investigation of bias due to prior knowledge of a positive PCR test showed that our main results are robust, with an overall burden of at least 1 symptom of 6.2 (95% CI, 3.5–8.6) per 100, more similar to previous estimates [12, 13].

One of the unique aspects of this study is the utilization of self-administered POCT to identify noninfected individuals. While the sensitivity of this test is relatively low, this step minimized the proportion of persons with prior SARS-CoV-2 infection among controls, strengthening our findings [19].

Current evidence indicates that vaccinations help reduce the risk of persistent symptoms after infection with SARS-CoV-2, yet there is still an urgent need to better understand long COVID's long-term impact and differences between SARS-CoV-2 variants [29, 30]. As long COVID seems to be prevalent and highly faceted, with a strong impact on both physical and mental health, informed interdisciplinary management strategies, treatments, and preventive measures are urgently needed.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Author contributions. The study was originally conceptualized by S. D. N., B. A., K. K. I., R. L. S., H. U., K. M., T. B., K. F., and B. F. S. Data collection was done by S. E., K. F., K. K. I., H. U., U. W. S., A. K., and B. F. S. Statistical analysis and visualization was done by M. v. W. All authors took part in conceptualization and discussion of results. M. v. W., S. E., and K. K. I. had full access to the data. The first draft of the manuscript was written by M. v. W., S. E., A. I. V. S., K. K. I., H. N., L. Ø., B. A., L. S., R. L. S., and S. D. N. All authors have critically revised the manuscript, approved of its final version, and agree to be accountable for all aspects of the work.

Patient consent. This study was performed as a national surveillance study under the authority task of the Danish national infectious disease control institute, Statens Serum Institut (SSI), Copenhagen, Denmark, and in collaboration with a consortium of Danish research institutions. According to Danish law, national surveillance activities from the SSI do not require approval from an ethics committee. In the invitation letter, participants were informed about their rights, including the right to withdraw from the study and have their submitted data deleted. The study was performed in agreement with the Helsinki II declaration and registered with the Danish Data Protection Agency (P-2020-901). Participation was strictly voluntary, no incentives were given, and all data were self-reported. All personal data obtained through the Enalyzer tool were kept in accordance with the general data protection regulation and data protection law stated by the Danish Data Protection Agency.

Data sharing. Data were collected for the purpose of the Testing Denmark study only and cannot be shared due to data protection regulations. Part of the data may however, be made available in a de-identified format for access to members of the scientific and medical community for noncommercial use only, by contacting the authors.

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