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Summary

Background Although the persistence of physical symptoms after SARS-CoV-2 infection is a major public health concern, evidence from large observational studies beyond one year post diagnosis remain scarce. We aimed to assess the prevalence of physical symptoms in relation to acute illness severity up to more than 2-years after diagnosis of COVID-19.

Methods This multinational study included 64,880 adult participants from Iceland, Sweden, Denmark, and Norway with self-reported data on COVID-19 and physical symptoms from April 2020 to August 2022. We compared the prevalence of 15 physical symptoms, measured by the Patient Health Questionnaire (PHQ-15), among individuals with or without a confirmed COVID-19 diagnosis, by acute illness severity, and by time since diagnosis. We additionally assessed the change in symptoms in a subset of Swedish adults with repeated measures, before and after COVID-19 diagnosis.

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Findings During up to 27 months of follow-up, 34.5% participants (22,382/64,880) were diagnosed with COVID-19. Individuals who were diagnosed with COVID-19, compared to those not diagnosed, had an overall 37% higher prevalence of severe physical symptom burden (PHQ-15 score ≥15, adjusted prevalence ratio [PR] 1.37 [95% confidence interval [CI] 1.23–1.52]). The prevalence was associated with acute COVID-19 severity: individuals bedridden for seven days or longer presented with the highest prevalence (PR 2.25 [1.85–2.74]), while individuals never bedridden presented with similar prevalence as individuals not diagnosed with COVID-19 (PR 0.92 [0.68–1.24]). The prevalence was statistically significantly elevated among individuals diagnosed with COVID-19 for eight of the fifteen measured symptoms: shortness of breath, chest pain, dizziness, heart racing, headaches, low energy/fatigue, trouble sleeping, and back pain. The analysis of repeated measurements rendered similar results as the main analysis.

Interpretation These data suggest an elevated prevalence of some, but not all, physical symptoms during up to more than 2 years after diagnosis of COVID-19, particularly among individuals suffering a severe acute illness, highlighting the importance of continued monitoring and alleviation of these targeted core symptoms.

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Keywords: Physical symptom; Long covid; Cohort; COVID-19

Research in context

Evidence before this study

As the majority of the global population has contracted COVID-19, persistence of physical symptoms after SARS-CoV-2 infection (*Long* COVID or post COVID-19 condition) has become a major public health concern. We searched PubMed for studies assessing physical symptoms after COVID-19, published by August 23, 2023. The search term was (physical symptoms after covid) AND LitCLONGCOVID [Pubmed filter]. We reviewed 99 studies, after excluding those not on humans or not published in English. High prevalence of multiple physical symptoms, mainly fatigue, shortness of breath, headache, muscle and chest pain, has been reported, mostly based on selected populations, samples of hospitalized patients confined to three months to one year after diagnosis. A comprehensive assessment of long-term prevalence of physical symptoms beyond one year after diagnosis and among non-hospitalized patients is lacking.

Added value of this study

We included 64,880 participants from the general population of four Nordic countries, of whom 22,382 had been diagnosed with COVID-19 up to 2 years earlier (<1% hospitalized due to COVID-19). Individuals diagnosed with COVID-19 reported a 37% higher prevalence of overall severe physical symptom burden compared to individuals not diagnosed with COVID-19. We found that shortness of breath, chest pain, dizziness, headaches, and low energy/fatigue were particularly increased among individuals with COVID-19 diagnosis. Individuals bedridden for seven days or more during the acute illness phase (9.6% of the patients) showed the greatest and most persistent elevation in prevalence of severe physical symptoms while individuals not bedridden during the acute COVID-19 illness showed no increase in prevalence of physical symptoms compared to those not diagnosed.

Implications of all the available evidence

Our findings provide timely and valuable evidence to demonstrate the constitution of Long COVID and the long-term health consequences after recovery from COVID-19 in the general population. The long-term risk of severe physical symptom burden is distinctly associated with acute illness severity, highlighting the importance of sustained monitoring of physical symptoms among the group of patients who suffered severe acute illness course.

Introduction

The COVID-19 pandemic continues to have substantial public health consequences three years after its outbreak in 2020. As of August 2023, more than 694 million individuals worldwide have been infected by the SARS-CoV-2 virus[1] and an estimated 10–20% of these individuals will continue to experience a variety of symptoms after recovery.[2] The presence of long-term symptoms persisting beyond two months after infection has been recognized as *Long* COVID or post-COVID-19 condition.[3,4] In addition to flu-like symptoms, studies suggest that other physical symptoms can

extend beyond the disease course,[4–7] including fatigue,[4,5,7] shortness of breath,[4,7] headache,[8,9] and myalgias and chest pain.[4,8,9] Many observational studies are based on small patient samples or selected populations,[10,11] with less than one year of follow-up post-diagnosis and, notably, focused on hospitalized patients.[7] General population data on the prevalence of physical symptoms after COVID-19 diagnosis over a longer period of time is lacking, especially by measures of acute illness severity.[8,9] Importantly, the absence of comparison to populations without a confirmed COVID-19 diagnosis has largely limited the interpretation of these findings.[4,8,11] Also, the use of validated instruments to quantify physical symptom severity is needed because assessment of individual physical symptoms has varied greatly in the literature,[5,7,8] making it difficult for direct comparisons.

With this background, we leveraged data from four *Nordic* cohorts of the COVIDMENT Consortium[12] to investigate the prevalence of physical symptom burden up to 27 months following a COVID-19 diagnosis with a focus on analysing the severity of acute COVID-19 illness and time since diagnosis. We further utilized repeated measures of the physical symptoms to assess the change in the prevalence of physical symptoms before and after COVID-19 diagnosis in a subset of adult study participants in Sweden.

Methods

Study population and design

We included four cohorts from the COVIDMENT Consortium with data collection on physical symptoms: 1) The Icelandic COVID-19 National Resilience Cohort (C-19 Resilience), which was established in April 2020 with two waves of data collection through August 2021. All adult Icelandic and English-speaking individuals who had an Icelandic electronic ID were eligible for participation. The C-19 Resilience cohort is over-represented by women, with a higher age and education than the general population; 2) The Swedish Omtanke2020 Study was established in June 2020, and collected monthly data on physical symptoms from July 2021 to February 2022, with yearly follow-ups thereafter. Eligible participation was all adult residents of Sweden with the electronic identification BankID. Omtanke2020 is over-representative of women, ages 40–69 years, and individuals living in an urban area; 3) The Norwegian COVID-19, Mental Health and Adherence Project (MAP-19) is a 9-wave longitudinal study initiated from March 2020, with additional information on physical symptoms collected in March 2022. It recruited adult residents across all age groups, and was found to be representative of the Norwegian adult population[13]; and 4) The Danish Blood Donor Study (DBDS) is an ongoing nationwide cohort study including blood doners at the time of blood donation.[12] Additional questionnaires were sent out to participants regarding long-term health changes related to COVID-19 from June to August 2022. The DBDS is slightly over-sampled by men, individuals of higher age and education. All study participants from the four cohorts provided electronic informed consent. Ethical approvals were obtained for each participating cohort from national or regional bioethics committees (Supplementary Table S1). After exclusion of study participants with incomplete information on COVID-19 diagnosis and incomplete assessment of physical symptoms, 64,880 individuals were included for further analysis: N = 14,358 from C-19 Resilience, N = 18,190 from the Omtanke2020, N = 3310 from MAP-19, and N = 29,958 from the DBDS (Supplementary Figure S1 flowchart).

Data collection and assessment

COVID-19 diagnosis was assessed by self-reported SARS-CoV-2 infection from a positive RT-PCR test. Participants who reported a confirmed diagnosis of COVID-19 during the study period were referred to as the COVID group whereas the remaining participants were referred to as the non-COVID group. Time since diagnosis was defined as the time interval between the reported date of diagnosis and physical symptom data collection, and was coded as 0–2 months, 3–5 months, 6–9 months, and 10–27 months (up to 16 months in C-19 Resilience, up to 22 months in Omtanke2020, up to 24 months in MAP-19, and up to 27 months in DBDS). The illness severity during the acute phase of COVID-19 was determined by self-reported number of days confined to bed (administered options in questionnaire: not bedridden, bedridden 1–6 days, or bedridden 7 days or longer), and hospitalization due to COVID-19 infection (yes or no), in line with our previous work.[14]

All four cohorts used the 15-item Patient Health Questionnaire (PHQ-15) to measure the severity of physical symptoms most commonly recognized in outpatient settings. The questionnaire was harmonized and administrated in the language of the respective country of each cohort. The PHQ-15 is a widely used instrument and has been validated in different populations.[15] Each symptom is scored as 0 ("not bothered at all"), 1 ("bothered a little"), or 2 ("bothered a lot").[16] Consistent with previous studies, a cut-off of PHQ-15 score ≥15 was defined as experiencing *severe physical symptom burden* (termed as severe symptoms) in our study, as this score indicates severe symptomology.[16,17] We used multiple imputation to estimate the individual physical symptom responses for participants who had missing values in the 15 items (missingness up to 25%, or 4 responses, per individual). Multiple imputation was performed using the R package MICE in C-19 Resilience and DBDS, using predictive mean matching method.[18] In Omtanke2020, multiple imputation was performed in SAS using proc mi using the fully conditional specification (FCS) regression method.[19] Those

with more than 25% missingness in the PHQ-15 were excluded from the analysis. Because data on physical symptoms was collected prospectively, we used assessments since enrolment for the non-COVID group, and since diagnosis for the COVID group.

Several covariates were included in the analysis, when available (Supplementary Table S1). The included covariates were age (discrete numeric in years), gender (male, female, or other), average monthly income (low, low-medium, medium, medium-high, or high income; not available in Omtanke2020), residency (capital or elsewhere), relationship status (single or in a relationship; not available in DBDS), body mass index (BMI, categorized as <25 kg/m^2 [normal or underweight], 25–30 kg/m^2 [overweight], or >30 kg/m^2 [obese]), current smoking (no or yes), habitual drinking (no or yes), history of psychiatric disorder (no or yes), pre-existing somatic comorbidity (no, one or more comorbidities), and response period (June 2020 or earlier, July–September 2020, October–December 2020, January–March 2021, April–June 2021, July–September 2021, October–December 2021, or January 2022 or after). We also included variables of current mental health status measured at the same survey (no or yes) for potential depression (Patient Health Questionnaire (PHQ-9)), anxiety (General Anxiety Disorder (GAD-7)) and COVID-19-related distress symptoms (Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) and the PTSD checklist for DSM-5; not available in DBDS), as described in our previous study.[14] Covariates with missing values were grouped as a separate level.

Statistical analysis

We first described the distribution of the above covariates between the COVID group and non-COVID group, as well as by acute illness severity and time since diagnosis for the COVID-19 group. We conducted a cross-sectional analysis comparing the prevalence of severe symptoms (PHQ-15 ≥15) in the COVID group, overall and by illness severity (bedridden and hospitalization) and time since diagnosis, to that of the non-COVID group. We applied a robust (modified) Poisson regression model to estimate prevalence ratios (PRs) with 95% confidence intervals (CIs), with a quasi-likelihood model used to fit a binary outcome.[20] A sandwich estimator with exchangeable working correlation structure was applied in the model to control for intra-individual correlation when repeated measures were available.[21] The PRs were calculated in crude models and then in adjusted models controlling for age, gender, average monthly income, residency, relationship status, BMI, current smoking, habitual drinking, previous diagnosis of psychiatric disorder, pre-existing somatic comorbidity, and response period. Covariates not measured in an individual cohort were not adjusted for in the analysis of that cohort. All analyses were performed among individuals with complete information on variables. We also stratified by gender, age, mental health indicators, and pre-existing somatic comorbidity to investigate if these factors would modify the association between COVID-19 and severe symptoms. To evaluate the influence of vaccination on physical symptoms, we further calculated the PR in C-19 Resilience and Omtanke2020 cohorts by restricting the analysis to those ever reported being partly or fully vaccinated. To investigate of the associations for individual symptoms, we estimated PRs for the 15 measured symptoms individually, analysing separately reporting being "bothered a little" or being "bothered a lot". The Bonferroni correction method was used to correct the P values for multiple testing. The analysis of PRs for reporting "bothered a lot" was further performed by illness severity and by time since diagnosis.

In the Swedish Omtanke2020 Study, a subset of individuals with a COVID-19 diagnosis had repeated measures of physical symptoms: one *prior to* and one following their COVID-19 diagnosis (N = 398). We conducted a pairwise analysis assessing the prevalence of individual symptoms comparing post-COVID (first response after diagnosis) to pre-COVID (last response before diagnosis) measures, i.e., pre-/post-COVID comparison. The pre-COVID measure was collected before infection, and was used as the reference. The extension of the modified Poisson regression models mentioned above was performed to assess the difference in prevalence of individual symptoms between the two time-points.

We performed the above analyses using a standardized analysis protocol in all four cohorts, and finally, to combine aggregated data from the cohorts, we meta-analysed the output from each cohort with a random-effects model using the metafor package in R to estimate an overall result for all analyses.[22] Heterogeneity of the findings was examined using the I^2 statistic.[23] Data management was done in SAS (v9.4) in Omtanke2020. Statistical analyses were conducted in R (version 4.0.5). This study is reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. QS and UAV had full access to the Icelandic data, EEJ and FF had full access to the Swedish data, OVE and SUJ had full access to the Norwegian data, MD and OBVP had full access to the Danish data, and take responsibility for the integrity and the accuracy of the data in the respective cohort. The corresponding authors had final responsibility for the decision to submit for publication, upon the approval from all authors.

Results

Baseline characteristics

Of the 64,880 participants, 22,382 (34.5%) reported having been diagnosed with COVID-19. Persons with

COVID-19 were younger, had a lower BMI, and had a lower proportion of pre-existing psychiatric disorder and somatic comorbidity, compared with the non-COVID group (Table 1). The demographics varied across the cohorts, with participants of MAP-19 being younger in age and more likely to be single than participants of other cohorts (Supplementary Table S2). Among persons with COVID-19, 28.0% were bedridden during acute infection (18.4% for 1–6 days; and 9.6% for 7 days or more) and 1.0% were hospitalized (Table 1).

Physical symptom burden

The distribution of PHQ-15 scores for COVID and non-COVID group were presented in Supplementary Figure S2. After dichotomizing the score, the prevalence of severe symptoms was higher among the COVID-19 group than the non-COVID group in all cohorts (Supplementary Table S3): 16.0% vs. 9.7% in C-19 Resilience, 8.0% vs. 5.5% in Omtanke2020, 8.5% vs. 7.6% in MAP-19, and 1.6% vs. 1.2% in DBDS, with MAP-19 and DBDS having larger proportion of participants infected with probable omicron variant (Supplementary Figure S3). Compared with the non-COVID group, individuals diagnosed with COVID-19 had an overall higher prevalence of severe symptoms during the entire study period, in each cohort as well as combined (overall adjusted PR 1.37 [95% CI 1.23–1.52], I^2 43.2%; P < 0.001) (Fig. 1). The prevalence increase was noted regardless of gender, age groups, existence of depressive, anxiety or COVID-19 related distress symptoms, or pre-existing somatic comorbidity (Supplementary Figure S4). As the majority of the participants reported being partly or fully vaccinated, we found similar increase in prevalence when restricting the analytic sample to vaccinated individuals (Supplementary Tables S4 and S5). Higher prevalence increase was observed for among individuals without depressive or anxiety symptoms (Supplementary Figure S4).

Longer time bedridden during acute infection was associated with a higher prevalence of severe symptoms in a dose-response manner, and the highest prevalence was consistently observed up to 27 months after diagnosis among participants bedridden for 7 days or more (combined results in Fig. 2 and by cohort in Supplementary Figure S5A). A higher prevalence was also observed among individuals hospitalized for COVID-19 from 2 months to 22 months following diagnosis (Supplementary Figure S5B).

When investigating individual symptoms, we found the most prevalent symptoms to be headaches, low energy/fatigue, joint pain, trouble sleeping, and back pain (Supplementary Table S6). Compared with the non-COVID group, we found that a COVID-19 diagnosis was associated with a higher prevalence of several symptoms (Fig. 3A), including being bothered a lot due to shortness of breath (PR 2.15 [1.37–3.38]), dizziness (PR 1.58 [1.41–1.76]), heart racing (PR 1.55 [1.27–1.89]), headaches (PR 1.38 [1.23–1.54]), and back pain (PR 1.10 [1.05–1.17]) as well as being bothered a little due to chest pain (PR 1.34 [1.15–1.56]), low energy/fatigue (PR 1.08 [1.04–1.13]), and trouble sleeping (PR 1.04 [1.02–1.06]). Elevations in the prevalence of similar symptoms were noted in individual cohorts except for DBDS, where less symptoms were identified (Supplementary Figure S6). We observed a consistently higher prevalence, particularly for individuals bedridden 7 days or longer or hospitalized for COVID-19, among 8 of the 15 measured symptoms (Fig. 4, Supplementary Table S7 and Supplementary Figure S7). There was no clear decline in the prevalence increase over time for most symptoms, except for dizziness where the prevalence increase declined over time.

Longitudinal analysis

The pairwise analysis of the subset of Omtanke2020 adult participants with pre- and post-COVID-19 measures of physical symptoms (n = 398, mean time interval = 3.2 months) largely confirmed the results of our cross-sectional analysis. As compared to before diagnosis, we observed an elevation of being bothered a lot due to headaches (PR 2.03 [1.64–2.54]) and low energy/fatigue (PR 1.36 [1.22–1.53]) after diagnosis of COVID-19 as well as being bothered a little due to shortness of breath (PR 1.45 [1.15–1.82]), chest pain (PR 1.76 [1.36–2.27]) and dizziness (PR 1.46 [1.22–1.74]) after diagnosis of COVID-19 (Fig. 3B).

Discussion

In this multinational observational study, we found an association between COVID-19 and persistence of severe physical symptoms during the follow-up from diagnosis to up to 27 months thereafter. Overall, persons diagnosed with COVID-19 had a 37% higher prevalence of severe symptoms compared with those not diagnosed. The association was strongly modified by acute COVID-19 illness severity, as the prevalence increase was particularly great among individuals who were bedridden 7 days or more. The higher prevalence was observed for multiple symptoms, in particular shortness of breath, chest pain, dizziness, headaches, and low energy/fatigue. This finding was similarly identified in a longitudinal analysis comparing severe symptoms *before* and *after* diagnosis in Sweden. The persistently increased prevalence of multiple symptoms more than two years following severe COVID-19 demonstrates the importance of a sustained monitoring of targeted physical symptoms in this patient group.

Long-term sequela following COVID-19 have been discussed continuously since the beginning of the pandemic. However, inconsistent definitions of post-COVID condition and a lack of comparison to individuals without COVID-19 diagnosis have made it

	Individuals *NOT* diagnosed with COVID-19 N (%)	Individuals diagnosed with COVID-19 N (%)
Total	42,498	22,382
C-19 Resilience (IS)	13,284 (31.0%)	1074 (4.7%)
Omtanke2020 (SE)	14,841 (34.7%)	3349 (14.5%)
MAP-19 (NO)	1701 (4.0%)	1609 (7.0%)
DBDS (DK)	12,672 (29.6%)	16,350 (71.0%)
Gender		
Male	13,290 (31.3%)	8507 (38.0%)
Female	29,114 (68.5%)	13,856 (61.9%)
Other	80 (0.2%)	13 (0.1%)
Missing	14 (<0.1%)	6 (<0.1%)
Age		
Mean, years (SD)	54 (14.7)	49 (11.7)
18–29 years	3334 (7.8%)	2617 (11.7%)
30–39 years	5117 (12.0%)	3771 (16.8%)
40–49 years	6776 (15.9%)	4696 (21.0%)
50–59 years	9979 (23.5%)	5510 (24.6%)
60–69 years	10,309 (24.3%)	4005 (17.9%)
70 years or older	6968 (16.4%)	1776 (7.9%)
Missing	14 (<0.1%)	7 (<0.1%)
Average monthly income		
Low income	5499 (12.9%)	2786 (12.4%)
Low-medium income	6261 (14.7%)	3815 (17.0%)
Medium income	6362 (15.0%)	4463 (19.9%)
Medium-high income	4731 (11.1%)	3605 (16.1%)
High income	3606 (8.5%)	3848 (17.2%)
Missing	1198 (2.8%)	516 (2.3%)
Not measured[a]	14,841 (34.9%)	3349 (15.0%)
Residence[b]		
Capital area	21,544 (50.7%)	9752 (43.6%)
Elsewhere	20,735 (48.8%)	12,589 (56.2%)
Missing or abroad	219 (0.5%)	41 (0.2%)
Relationship status		
Single	7925 (18.6%)	1593 (7.1%)
In a relationship	21,660 (51.0%)	4380 (19.6%)
Missing	241 (0.6%)	59 (0.3%)
Not measured[a]	12,672 (29.8%)	16,350 (73.0%)
BMI (kg/m^2)		
<25 normal or low weight	17,591 (41.4%)	10,090 (45.1%)
25–30 overweight	14,904 (35.1%)	8035 (35.9%)
>30 obese	8708 (20.5%)	3858 (17.2%)
Missing	1295 (3.0%)	399 (1.8%)
Current smoking status		
No	36,848 (86.7%)	20,279 (90.6%)
Yes	5236 (12.3%)	2013 (9.0%)
Missing	414 (1.0%)	90 (0.4%)
Habitual drinking		
No	35,455 (83.4%)	18,584 (83.0%)
Yes	7043 (16.6%)	3798 (17.0%)
History of psychiatric disorder		
No	31,186 (73.4%)	18,472 (82.5%)
Yes	10,705 (25.2%)	3790 (16.9%)
Missing	607 (1.4%)	120 (0.5%)

(Table 1 continues on next page)

	Individuals *NOT* diagnosed with COVID-19 N (%)	Individuals diagnosed with COVID-19 N (%)
(Continued from previous page)		
Pre-existing comorbidity		
No	30,027 (70.7%)	18,299 (81.8%)
Yes	12,156 (28.6%)	3964 (17.7%)
Missing	315 (0.7%)	119 (0.5%)
Current depressive symptoms[c]		
No	36,174 (85.1%)	19,397 (86.7%)
Yes	5446 (12.8%)	2644 (11.8%)
Missing	878 (2.1%)	341 (1.5%)
Current anxiety symptoms[d]		
No	38,805 (91.3%)	21,146 (94.5%)
Yes	3360 (7.9%)	1209 (5.4%)
Missing	333 (0.8%)	27 (0.1%)
Current COVID-19 related distress symptoms[e]		
No	21,531 (50.7%)	4840 (21.6%)
Yes	7961 (18.7%)	1163 (5.2%)
Missing	334 (0.8%)	29 (0.1%)
Not measured[a]	12,672 (29.8%)	16,350 (73.0%)
Response period		
June 2020 or earlier	12,744 (30.0%)	235 (1.0%)
July–September 2020	136 (0.3%)	6 (0.0%)
October–December 2020	363 (0.9%)	178 (0.8%)
January–March 2021	37 (0.1%)	618 (2.8%)
April–June 2021	4 (0.0%)	37 (0.2%)
July–September 2021	10,072 (23.7%)	1434 (6.4%)
October–December 2021	1970 (4.6%)	423 (1.9%)
January 2022 or after	17,172 (40.4%)	19,451 (86.9%)
Illness severity—time bedridden		
Not bedridden	–	15,027 (67.1%)
Bedridden 1–6 days	–	4127 (18.4%)
Bedridden 7 days or more		2148 (9.6%)
Missing		1080 (4.8%)
Illness severity—hospitalization		
Not hospitalized	–	20,670 (92.4%)
Hospitalized	–	230 (1.0%)
Missing or not measured		1482 (6.6%)
Time since COVID-19 diagnosis		
0–2 months	–	3150 (14.1%)
3–5 months	–	10,879 (48.6%)
6–9 months	–	4822 (21.5%)
>10 months	–	3242 (14.5%)
Missing	–	289 (1.3%)
Vaccination status[f]		
None	1358 (3.2%)	1074 (4.8%)
Partly or fully vaccinated	35,820 (84.3%)	20,329 (90.8%)
Missing	5320 (12.5%)	979 (4.4%)

[a]Average monthly income was not measured in Omtanke2020 (SE). Relationship status and current COVID-19-related distress symptoms were not measured in DBDS (DK). [b]*Missing or abroad* refers to either missing in four cohorts or reported as living abroad in C-19 Resilience (IS). [c]Current depressive symptoms were measured using Patient Health Questionnaire (PHQ-9), with recommended cut-off of ≥10 indicating *Yes* to potentially having this condition in all cohorts. [d]Current anxiety symptoms were measured using General Anxiety Disorder (GAD-7) in C-19 Resilience (IS), Omtanke2020 (SE) and MAP-19 (NO), while measured by Angst-Symptom-Spørgeskemaet (ASS) in DBDS (DK), with a recommended cut-off of ≥10 indicating *Yes* to having this condition. [e]Current COVID-19-related distress symptoms were measured using the modified Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) with a recommended cut-off of ≥4, and the PTSD checklist for DSM-5 (PCL-5), indicating *Yes* to having this condition. [f]Evaluated at the time of physical symptom response.

Table 1: **Background characteristics of 64,880 study participants *NOT* diagnosed or diagnosed with COVID-19.**

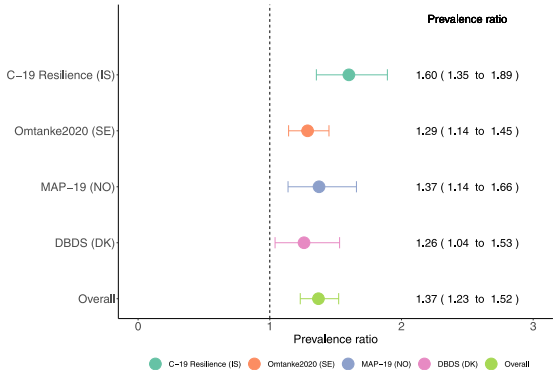

Fig. 1: **Prevalence ratio (95% confidence interval) of severe physical symptom burden (PHQ-15 ≥15) among individuals with COVID-19 compared with individuals *NOT* diagnosed with COVID-19 in the four cohorts, and a meta-analysis (I^2 43.2%)[a].** [a]Prevalence ratios were adjusted for age, gender, residency, average monthly income, current smoking, BMI, pre-existing comorbidity, relationship status, habitual drinking, previous diagnosis of psychiatric disorder, and response period. Income was not available in Omtanke2020 (SE), and relationship status was not available in DBDS (DK).

difficult to comprehensively assess the long-term health impact of this infection. To our knowledge, this is one of the few largest cohort studies to quantify risks of common physical symptoms among individuals diagnosed with COVID-19 in the general population using

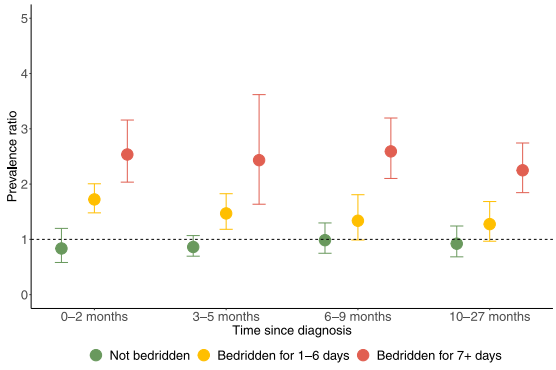

Fig. 2: **Prevalence ratio (95% confidence interval) of severe physical symptom burden (PHQ-15 ≥15) among people with COVID-19 compared with people *NOT* diagnosed with COVID-19, by illness severity (bedridden) according to time from diagnosis, a meta-analysis combining four cohorts[a].** [a]Number of study subjects per group is located in Supplementary Table S3. Individuals with missing information on time since diagnosis or illness severity were excluded from this analysis (as shown in Table 1). Prevalence ratios were adjusted for age, gender, residency, average monthly income, current smoking, BMI, pre-existing comorbidity, relationship status, habitual drinking, previous diagnosis of psychiatric disorder, and response period. Income was not available in Omtanke2020 (SE), and relationship status was not available in DBDS (DK).

validated assessment tool. Our finding of increased risk of long-term severe symptoms is consistent with previous studies mostly based on hospitalized patients[24] with a relatively short follow-up time of below[25–27] or around[28] one year, and without a comparison to the population free of COVID-19.[4,25,26,28] Consistent with our previous study,[14] we utilized self-reported number of days bedridden in addition to hospitalization as a proxy for illness severity. As a result, we assessed severity of the acute phase of COVID-19 among non-hospitalized patients (92.4% of the COVID), which is usually not targeted in existing studies.[7,29] Individuals with severe acute COVID-19, particularly those who were bedridden 7 days or longer (9.6% of the COVID group) or hospitalized (1.0% of the COVID group), had a greater increase in prevalence of severe symptoms, while those with a milder infection (not bedridden at all) showed none or only a marginal (bedridden 1–6 days) increase in such prevalence. The finding on no risk increase among persons with milder infection was not in line with previous reports from early in the Pandemic[30] or where only hospitalization has been used as proxy of illness severity.[5] Inconsistent with previous findings showing higher risk in women,[9] we noted comparable prevalence increase in physical symptom burden among males and females. These differences in finding may be, at least partly, be due to reliance on electronic health records in many previous reports indicating increased health care seeking behaviour among women after COVID-19[31] while the direct symptom assessments in our study suggests comparable rise in physical symptom prevalence across genders. We found an even higher prevalence increase for individuals without depression or anxiety symptoms indicating that the association between severe acute COVID-19 illness and risks of long-term physical symptoms may be independent of such mental health symptomology. The long-term health impact of severe COVID-19 is consistent with a recent hospital-based study from Italy, showing highly elevated prevalence in symptoms one year after acute illness.[28] The ultimate duration of the risk increase remains unclear, and studies including long-term follow-ups are needed. Research from previous coronavirus outbreaks indeed indicates similar persistence of physical symptoms among survivors of SARS-CoV-1 (SARS), Middle East respiratory syndrome coronavirus (MERS), and acute respiratory distress syndrome (ARDS), including musculoskeletal pain, chronic fatigue, and exercise intolerance up to 5 years after infection.[32–35]

Similar to previous studies,[4–7,9,25,36,37] our findings indicate that shortness of breath, headaches, chest pain, dizziness, and low energy/fatigue may be core symptoms of Long COVID. The comparison on the magnitude of the increase in specific symptoms is difficult across studies that lack a proper comparison to individuals without COVID-19,[4,29] as well as use different methods to quantify the symptoms. The findings on

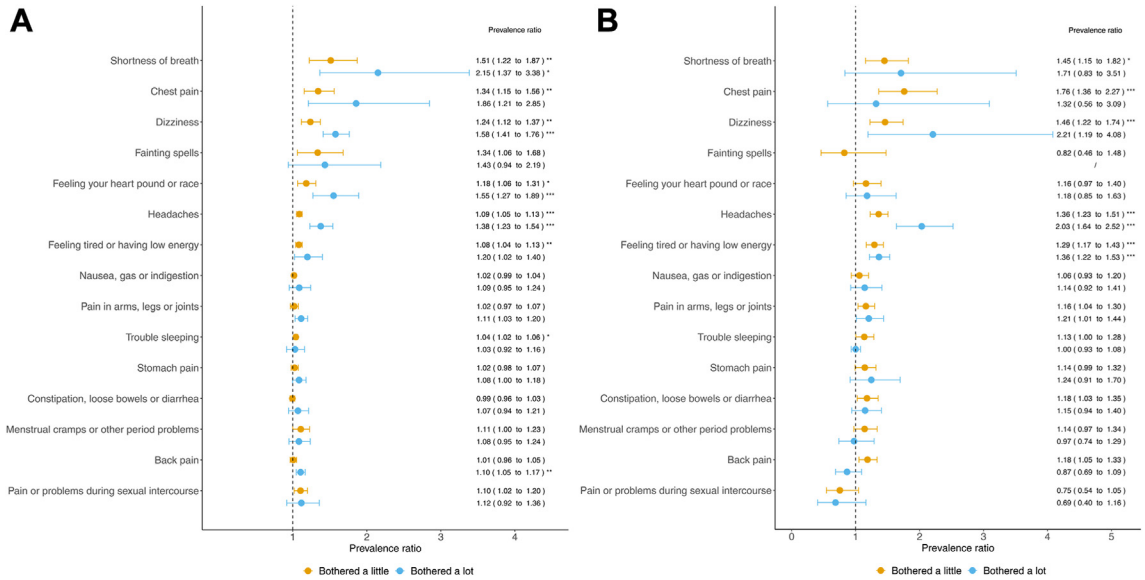

Fig. 3: **Prevalence ratio (95% confidence interval) of individual physical symptom severity among people with COVID-19 compared with those *NOT* diagnosed with COVID-19, by each physical symptom[a].** A. COVID-to-non-COVID cross-sectional comparison (all cohorts). B. Post-to-Pre COVID longitudinal comparison (Omtanke2020, N = 398). [a]Prevalence ratios were adjusted for age, gender, residency, average monthly income, current smoking, BMI, pre-existing comorbidity, relationship status, habitual drinking, previous diagnosis of psychiatric disorder, and response period. Income was not available in Omtanke2020 (SE), and relationship status was not available in DBDS (DK). Menstrual cramps were only applied to women aged <60 years. P-values were corrected for multiple testing using Bonferroni correction method. *Indicates corrected P-value <0.05; **<0.01; ***<0.001.

sustained increased prevalence of various symptoms after COVID-19, particularly after a severe course of acute illness, may be explained by several potential mechanisms. Although hyperactivity of proinflammatory cytokine response during the acute stage of the infection is observed,[38] the chronic inflammation following the acute disease phase is more likely to be associated with the persistent physical symptoms over 2 years. The circulating anti-nuclear autoantibodies are reported to form for individuals with COVID-19,[39–41] which cause inflammation and damage to multi-organs, leading to various autoimmune diseases. For instance, elevated levels of IL-1β, IL-6, IL-8 and TNF-α persisting after recovery from COVID-19 infection have been suggested to cause long-term COVID-19 symptoms.[39] The chronic inflammation following acute infection can lead to alveolar damage in the lungs as well as microvascular injury.[38,42] Also, there is suggestive evidence that some individuals do not completely clear the virus over time, resulting in persistent viral load in the body and chronic symptoms.[43] Similar mechanisms have been found in other inflammatory diseases, such as rheumatoid arthritis where prolonged elevated TNF-α has been associated with development of fatigue. Taken together, the prolonged symptoms following COVID-19 are likely to manifest multi-organ involvement,[44] although these mechanisms are not fully understood. Further research is therefore needed to understand the long-term effects of the infection whereas sustained clinical surveillance on long-lasting physical symptoms is needed, by taking into account acute illness severity and time since diagnosis. The heterogeneity of the reported COVID-19 associated physical symptoms from existing literatures challenges the understanding of underlying pathophysiology. Thus, our findings shed further lights on narrowing the range of these symptoms and, thereby, basis for more for targeted surveillance and interventions, as well as resource allocation from the policy point of view.

Strengths and limitations

The strengths of our study include the large sample size with more than 22,000 persons diagnosed with COVID-19 with varying acute illness severity, as well as a large comparison group without COVID-19, across four Nordic countries. We were able to use detailed information on illness severity and time since diagnosis to investigate the association according to illness severity over time, with adjustment for a list of selected covariates. The validated questionnaire used to quantify the severity of physical symptoms enabled us to comprehensively assess the severe physical symptom burden, overall and individually. The more than 2-year follow-up provided, so far, the longest assessment on risk of persistent severe symptoms after infection with SARS-CoV-2. We were able to directly compare severe

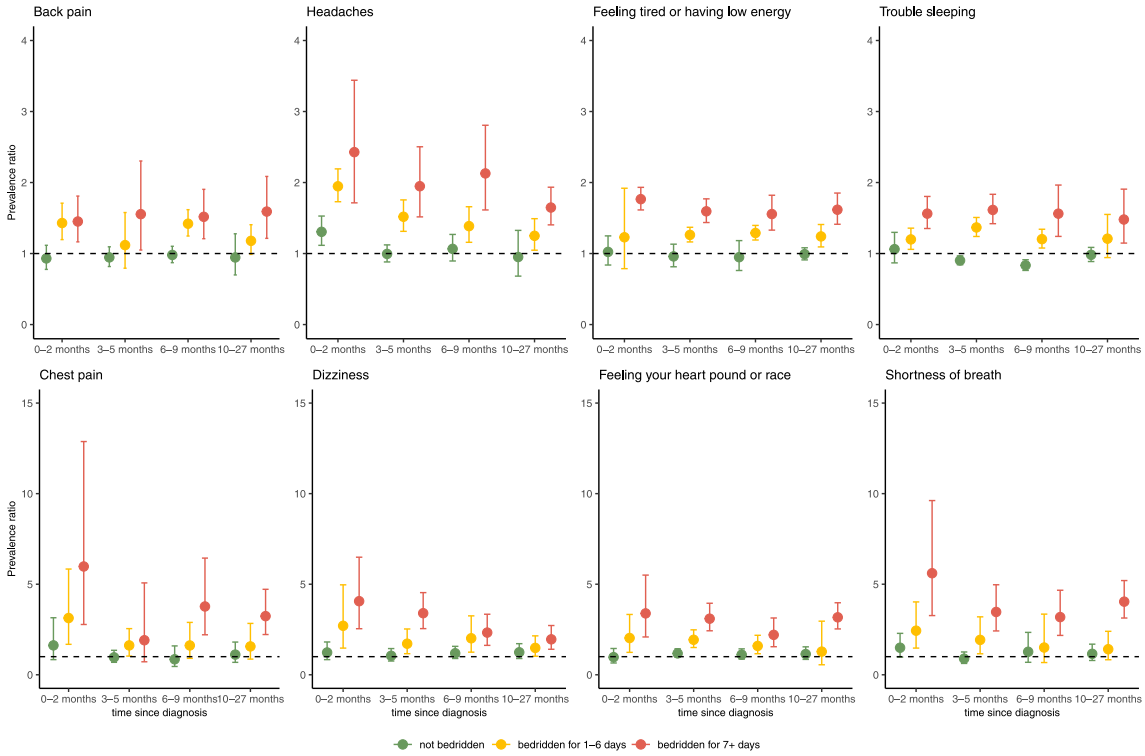

Fig. 4: **Prevalence ratio (95% confidence interval) of reporting *bothered a lot* to each symptom among people with COVID-19 compared with those *NOT* diagnosed with COVID-19 in C-19 Resilience, Omtanke2020 and DBDS, by illness severity (bedridden) according to time from diagnosis[a].** [a]Prevalence ratios were adjusted for age, gender, residency, average monthly income, current smoking, BMI, pre-existing comorbidity, relationship status, habitual drinking, previous diagnosis of psychiatric disorder, and response period. Income was not available in Omtanke2020 (SE), and relationship status was not available in DBDS (DK).

symptoms before and after COVID-19 diagnosis in a subset of Omtanke2020 participants, demonstrating a longitudinal impact of acute illness on participant's physical health.

There are also some limitations to be noted. First, our study relies on self-reported information on COVID-19 diagnosis and physical symptoms, and therefore may suffer from recall bias, meaning that participants may not remember all the details of their illness. This will likely have diluted the results toward null. Second, individuals with COVID-19 may be more prone to report symptoms than the non-COVID group. Yet, the null association observed in the group who were diagnosed with COVID-19 but were not bedridden alleviates this concern to some extent. Third, the varying time periods of data collection in the four cohorts coinciding with the different pandemic waves and respectively different virus variants may result in substantial differences across cohorts in comparisons of physical symptoms between COVID and non-COVID groups. We adjusted for the response period in the multivariable models to control for this discrepancy and the similar positive associations noted across the four cohorts argue against our findings being explained entirely by these factors. The smaller prevalence increase in DBDS and MAP-19 may be due to the larger proportion of participants likely infected with the omicron variant, than other cohorts, this coincides with a higher likelihood of being partly or fully vaccinated in these data collection waves (Supplementary Figure S3). Fourth, despite consistent positive overall associations noted in each cohort, we found the prevalence increase of severe symptoms to be smaller in DBDS than C-19 Resilience (26% vs. 60% increase in prevalence). The DBDS cohort is comprised of active or former blood donors, presumably healthier than the general population. This healthy donor effect may partly explain the smaller prevalence increase observed in DBDS, compared to the other cohorts, and may result in an underestimated overall association when combining results of all cohorts. Apart from the abovementioned differences in the cohorts, the potential protective effect of the COVID-19 vaccine might also have played a role in participants with a late response period in Omtanke2020, MAP-19, and DBDS. Evidence has indeed shown reduced physical symptoms among fully vaccinated individuals.[28,45] The majority of the participants in each of these cohorts reported being partly or fully vaccinated, and sensitivity analysis in C-19

Resilience and Omtanke2020 showed largely similar results when restricting to vaccinated individuals only (Supplementary Tables S4 and S5). Lastly, our findings should be generalized with caution to other populations or countries with different societal, background, or healthcare systems than Nordic countries.

Conclusion

This multinational study of persons with COVID-19 in four Nordic countries indicates that severe acute illness of SARS-CoV-2 infection is an important predictor of persistent physical symptoms, e.g., shortness of breath, chest pain, dizziness, headaches, and low energy/fatigue, up to 27 months after diagnosis. These findings highlight the importance of continued monitoring and alleviation of the identified core physical symptoms, at least during the first 2 years after diagnosis, among individuals suffering severe forms of COVID-19.

Contributors

The participating COVIDMENT cohorts and/or their data collections were designed by QS, EEJ, OVE, MD, OBVP, SUJ, FF, UAV, and their respective teams. UAV, QS, and TA directed the combined effort of this study implementation. UAV, QS, EEJ, and TA designed the analytical strategy in close collaboration with all team members and all authors helped to interpret the findings. QS, EEJ, OVE, and MD conducted the literature review and drafted the manuscript under supervision of UAV. All authors revised the manuscript for critical content and approved the final version of the manuscript.

Data sharing statement

The individual-level data underlying this article were subject to ethical approval and cannot be shared publicly due to data protection laws in each participating country.

Declaration of interests

OAA receives support from the NordForsk (grant number 105668 COVIDMENT) and the European Union's Horizon 2020 Research and Innovation Programme (Grant 847776; CoMorMent). OAA declares receiving grants or contracts from NIH NIMN Award (R01MH123724-01, 1R01MH124839, 1R01MH129742, 1R01MH129858-01A1), Research Council of Norway (RCN grants 223273, 296030, 300309, 324252), the South-East Norway Health Authority (grant 2017-112, 2022-073), European Union's Horizon 2020 Research and Innovation Programme (Grant 964874 REALMENT), EEA-RO-NO-2018-0535, and KG Jebsen Stiftelsen (grants SKGJ-MED-008 and SKGJ-MED-021). OAA receives consulting fees from Biogen, Cortechs.ai and Milken. OAA gets Speaker's honorarium from Janssen, Lundbeck and Sunovion, and has a patent on Intranasal Administration (US20160310683 A1). OAA participated in advisory board as National PI for JANSSEN trial depression, MAPS trial PTSD and BI trial schizophrenia. OAA declares having stock at Cortechs.ai. RP receives grant of Excellence, Icelandic Research Fund. RP declares to be the vice president at UEMS Section of Internal Medicine, a board member of the Icelandic Society of Internal Medicine, and is the president of the Icelandic Transplantation Society. EF received a payment for keynote lecture from Astra Zeneca. SUJ is a leader in Metacognitive Therapy Institute Norwegian Branch. FF receives support from the NordForsk (grant number 105668 and 138929 COVIDMENT) and the Horizon 2020 (Grant 847776; CoMorMent). UAV receives support from the NordForsk (grant number 105668 and 138929 COVIDMENT) and the Horizon 2020 (Grant 847776; CoMorMent). AL declares to receive Fredrik and Ingrid Thuring Foundation. OBVP receives Independent Research Fund Denmark (0214-00127B). QS declares receiving support from the Outstanding Clinical Discipline Project of Shanghai Pudong (Grant No.: PWYgy2021-02) and the Fundamental Research Funds for the Central Universities. PFS declares receiving funding from the Swedish Research Council (Vetenskapsrådet, award D0886501). PFS also receives consulting fees, participating on a data safety monitoring board or advisory board, and holds stock or stock options, from Neumora Therapeutics. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2023.100756.

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