Acute COVID-19 severity and mental health morbidity trajectories in patient populations of six nations

Acute COVID-19 severity and mental health morbidity trajectories in patient populations of six nations: an observational study

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Summary

Background Long-term mental and physical health consequences of COVID-19 (long COVID) are a persistent public health concern. Little is still known about the long-term mental health of non-hospitalised patients with COVID-19 with varying illness severities. Our aim was to assess the prevalence of adverse mental health symptoms among individuals diagnosed with COVID-19 in the general population by acute infection severity up to 16 months after diagnosis.

Methods This observational follow-up study included seven prospectively planned cohorts across six countries (Denmark, Estonia, Iceland, Norway, Sweden, and the UK). Participants were recruited from March 27, 2020, to Aug 13, 2021. Individuals aged 18 years or older were eligible to participate. In a cross-sectional analysis, we contrasted symptom prevalence of depression, anxiety, COVID-19-related distress, and poor sleep quality (screened with validated mental health instruments) among individuals with and without a diagnosis of COVID-19 at entry, 0–16 months from diagnosis. In a cohort analysis, we further used repeated measures to estimate the change in mental health symptoms before and after COVID-19 diagnosis.

Findings The analytical cohort consisted of 247 249 individuals, 9979 (4·0%) of whom were diagnosed with COVID-19 during the study period. Mean follow-up was 5·65 months (SD 4·26). Participants diagnosed with COVID-19 presented overall with a higher prevalence of symptoms of depression (prevalence ratio [PR] 1·18 [95% CI 1·03–1·36]) and poorer sleep quality (1·13 [1·03–1·24]) but not symptoms of anxiety (0·97 [0·91–1·03]) or COVID-19-related distress (1·05 [0·93–1·20]) compared with individuals without a COVID-19 diagnosis. Although the prevalence of depression and COVID-19-related distress attenuated with time, individuals diagnosed with COVID-19 but never bedridden due to their illness were consistently at lower risk of depression (PR 0·83 [95% CI 0·75–0·91]) and anxiety (0·77 [0·63–0·94]) than those not diagnosed with COVID-19, whereas patients who were bedridden for more than 7 days were persistently at higher risk of symptoms of depression (PR 1·61 [95% CI 1·27–2·05]) and anxiety (1·43 [1·26–1·63]) than those not diagnosed throughout the study period.

Interpretation Severe acute COVID-19 illness—indicated by extended time bedridden—is associated with long-term mental morbidity among recovering individuals in the general population. These findings call for increased vigilance of adverse mental health development among patients with a severe acute disease phase of COVID-19.

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Introduction

Adverse mental health symptoms[1–3] and comorbid psychiatric disorders[3,4] among patients with COVID-19 have been documented up to 6 months after hospital discharge.[3,5,6] Yet, in addition to the reported methodological shortcomings of the existing literature on this topic (ie, inpatient samples and absence of comparison groups),[5,7] little is still known about the long-term mental health of non-hospitalised patients with COVID-19 with varying illness severities.

Both psychological and pathophysiological factors might contribute to mental health outcomes among patients diagnosed with COVID-19. First, the somewhat unpredictable disease course and prognosis,[8] worries of having infected others,[9] and extensive media coverage of long-term effects of the disease[10] might contribute to a transient rise in mental health symptoms. Second, the exacerbation of the COVID-19 illness resulting in severe influenza-like symptoms and associated pro-inflammatory processes[4] might contribute to the development of mental health symptoms among patients with a severe disease course[4,11] for, as yet, an unknown duration. Finally, several vulnerability factors, such as history of psychiatric disorders, might both be associated with the risk of a

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Research in context

Evidence before this study

There remain persistent concerns for long-term physical and mental health effects of SARS-CoV-2 infection (referred to as long or chronic COVID) among patients recovering from COVID-19. We searched PubMed on Dec 14, 2021, for publications in English on the mental health of those diagnosed with COVID-19, using the terms "COVID-19" AND ("mental health" OR "depression" OR "anxiety") with no restrictions on publication date. We excluded studies that did not report specifically on the mental health of those diagnosed with COVID-19. High symptom levels of depression and anxiety among patients with COVID-19 have been reported, mostly based on patients admitted to hospital due to COVID-19 within 6 months of diagnosis. We found no studies focusing on non-hospitalised patients with COVID-19 with varying illness severity beyond 6 months of diagnosis.

Added value of this study

To our knowledge, this is the first study on non-hospitalised patients with COVID-19 in the general population up to 16 months after diagnosis. Leveraging multiple cohorts from six north-European countries of 247 249 adult individuals, our findings suggest that acute COVID-19 illness severity is associated with long-term adverse mental health symptoms among patients in the general population. During the up to 16-month observation period of the study, 9979 individuals were diagnosed with COVID-19 (mostly outpatients) and although overall symptoms of depression and COVID-19-related distress attenuated over time from diagnosis, individuals who were bedridden for 7 days or more in the acute illness phase—representing 22·3% of the patient population—showed persistently high symptom levels of depression and anxiety throughout the observation period. By contrast, individuals who were never bedridden due to COVID-19 presented with lower risks of mental morbidities than non-infected individuals throughout the observation period.

Implications of all the available evidence

These findings have great implications for our understanding of long-term mental health symptom development in COVID-19, namely that the severity of acute COVID-19 illness modifies this risk. These results call for increased vigilance of adverse mental health among the substantial proportion of patients with a severe acute disease phase of COVID-19.

severe acute COVID-19 illness[12] and subsequent risks of adverse mental health symptoms.

Chronic COVID-19, or long COVID, has been referred to as persistence of physical and mental symptoms beyond 2 months after infection.[13,14] Indeed, one study has provided evidence for elevated risks of psychiatric disorders up to 6 months following COVID-19 regardless of whether patients were admitted to hospital or not.[2] However, few studies have explored mental health symptom development beyond 6 months after diagnosis of COVID-19 in the general population as well as to what extent varying acute infection severity in COVID-19 predicts long-term mental health symptomology. To this end, we leveraged the multinational and population-based COVIDMENT cohorts[15] to explore the mental health symptom trajectories up to 16 months after COVID-19 diagnosis. In line with the proposed underlying mechanisms summarised above, we hypothesised that mental health symptoms would generally decline with time from COVID-19 diagnosis (from when physical symptoms and uncertain prognosis could be expected to have resolved), whereas severe COVID-19 acute infection (indicated by number of days confined to bed [bedridden] due to COVID-19 symptoms) would be associated with persistent adverse mental health symptoms.

See Online for appendix

Methods

Study design and participants

This observational follow-up study included seven cohorts from six countries (Denmark, Estonia, Iceland, Norway, Sweden, and the UK) with harmonised data collections prospectively planned in March, 2020. These cohorts are all part of the COVIDMENT project, described elsewhere.[15] The cohorts used different strategies for recruitment, most recruiting from already established cohorts, whereas some also opened for self-recruitment through social media. The cohorts were: The Danish Blood Donor Study (DBDS, n=71 562), The Estonian Biobank COVID-19 Cohort (EstBB-C19, n=14 452), The Icelandic COVID-19 National Resilience Cohort (C19-Resilience, n=23 962), The Norwegian COVID-19, Mental Health and Adherence Project (MAP-19, n=10 061), The Norwegian Mother, Father and Child Cohort Study (MoBa, n=132 486), The Swedish Omtanke2020 (n=28 293), and the UK-based CovidLife (n=18 518).[15] Individuals aged 18 years and older were eligible to participate. All cohorts had ethical approvals from respective national or regional ethics committees (see appendix p 2) with varying numbers of waves of data collections from March 27, 2020, to Aug 13, 2021. All participants provided written or electronic informed consent.

We excluded individuals from the analyses if they did not have complete information on COVID-19 diagnosis and at least one of the four outcome variables.

Procedures

We used self-reports of a confirmed positive RT-PCR test (all cohorts) or positive antibody test (only in Omtanke2020) for SARS-CoV-2 infection as an indicator of a COVID-19 diagnosis (appendix p 2). Based on

reported calendar month of diagnosis, the time from diagnosis until data collection was coded as 0 to 2 months (0–56 days), more than 2 months to 6 months (57–180 days), or more than 6 months to 16 months (>180 days). To determine COVID-19 acute infection severity, we used the participants' reports of the number of days they were bedridden due to COVID-19. Participants were asked "How many days were you confined to bed due to COVID-19 symptoms?" with responses ranging from "Never" to "Seven days or longer". In EstBB-C19 only, we used self-reports of the number of days with fever. We also obtained information on hospital admission for COVID-19 (see appendix p 2).

Several validated mental health instruments, including screening measures for depressive symptoms (Patient Health Questionnaire with the recommended cutoff of ≥10[16] and Emotional State Questionnaire Depression subscale [EST-Q2] with the recommended cutoff of >11),[17,18] anxiety (Angst-Symptom-Spørgeskemaet, EST-Q2 Anxiety subscale[17] with the recommended cutoff of >11, and General Anxiety Disorder with the recommended cutoff of ≥10),[19] COVID-19-related distress (The Primary Care PTSD Screen for DSM-5 with the recommended cutoff of ≥4,[20] and the PTSD checklist for DSM-5),[21] and sleep quality (EST-Q2 Insomnia subscale[17] with the recommended cutoff of >5 and Pittsburgh Sleep Quality Index)[22] were included in all cohorts (see appendix p 2 for further information). All the screening measures for post-traumatic stress were modified to refer specifically to COVID-19 (eg, "Had nightmares about COVID-19?") and are therefore hereafter referred to as COVID-19-related distress.

Covariates were the following: gender (male, female, or other); age (continuous, in years); education (compulsory or less [no formal education]; upper secondary, vocational, or other; bachelor's or diploma university degree; and master's or PhD [information on education not available in Omtanke2020]); relationship status (in a relationship or single [information on relationship status not available in EstBB-C19]); history of diagnosis of any psychiatric disorder (yes or no) or chronic medical condition (defined as hypertension, diabetes, heart disease, lung disease, chronic kidney disease [information on chronic kidney disease not available in DBDS], cancer, immunosuppressive state [information on immunosuppressive state not available in DBDS], or immunosuppressive therapy [information on immunosuppressive therapy not available in DBDS]; no conditions; one condition; two conditions; more than two conditions); response periods (March–June, 2020; July–September, 2020; October–December, 2020; January–March, 2021; April–August, 2021; appendix p 2). Because body-mass index and smoking have both been associated with COVID-19[23,24] and mental morbidities,[25,26] we also included body-mass index (<25, 25–30, and >30 kg/m²) and smoking (never, former, or current) in all our models.

Statistical analysis

First, we explored the distribution of sociodemographic and health-related factors between individuals with and without a COVID-19 diagnosis for each cohort, individually and combined, along with symptom severity for individuals with a COVID-19 diagnosis. We then did a cross-sectional analysis contrasting the prevalence of mental health indicators among individuals with and without a diagnosis of COVID-19, overall and in subgroup analyses by illness severity and time from diagnosis.

Baseline measurements were used for individuals without a diagnosis of COVID-19, whereas the first measurement after diagnosis was used for the patients with COVID-19. All outcome variables were binary. We used robust (modified) Poisson regression models to estimate prevalence ratios (PRs) with 95% CIs. In robust Poisson regression, a quasi-likelihood model can be applied to fit the data with a binary outcome.[27] The exponential of the effect size can be interpreted as a relative risk or a PR.[28] This approach can be extended to repeated measures data.[29] We used classical sandwich estimator with exchangeable working correlation structure to control for intra-individual correlation when repeated measures were available.[29] We adjusted the estimates for age and gender in the first model, and in the second model additionally for education, relationship status, smoking, body-mass index, previous psychiatric diagnosis, number of chronic medical conditions, and response period. Cohorts that did not measure specific covariates excluded them from their models (appendix p 2). MoBa and MAP-19 had a high proportion of missing body-mass index and smoking data and used a missing indicator on these covariates to avoid dropping large numbers of participants from the analysis.

In a subpopulation with repeated symptom measures, we did a cohort analysis testing for potential change in symptom burden over time, from before and until after COVID-19 diagnosis. Among the Icelandic C19-Resilience, Norwegian MoBa, Swedish Omtanke2020, and the UK-based CovidLife cohorts, we did a pair-wise comparison of repeated measures of mental health outcomes at two timepoints among individuals with a COVID-19 diagnosis. Baseline measurements were the first response to a questionnaire after reporting a positive COVID-19 diagnosis, and the follow-up measurement was the last available response to a questionnaire. The aforementioned extension of the modified Poisson regression models was done to test the difference of the mental health outcomes between the two timepoints, while adjusting for response period. We did a similar comparison of mental health measures at two timepoints for individuals who answered at least one questionnaire before being diagnosed with COVID-19 and at least one questionnaire after being diagnosed. The baseline measurement was the last questionnaire before a COVID-19 diagnosis and the follow-up measurement was the first questionnaire in which a COVID-19 diagnosis was reported.

We meta-analysed based on aggregated data from each cohort with a random-effects model using the metafor package in R to estimate overall PRs for all the aforementioned analyses.[30] Heterogeneity for each overall mental health outcome was examined using the I^2 statistic.[31] Statistical analyses were done in R (version 4.1.1), SAS (version 9.4), and Stata (version 17.0). Our study is reported according to the Strengthening the Reporting of Observational studies in Epidemiology checklist (appendix pp 25–27).

	COVID-19 diagnosis (n=9979)	No COVID-19 diagnosis (n=237 270)
DBDS (Denmark)	1111 (11·1%)	29 806 (12·6%)
EstBB-C19 (Estonia)	2121 (21·3%)	7868 (3·3%)
C19-Resilience (Iceland)	1144 (11·5%)	20 471 (8·6%)
MAP-19 (Norway)	110 (1·1%)	9951 (4·2%)
MoBa (Norway)	1995 (20·0%)	130 456 (55·0%)
Omtanke2020 (Sweden)	3175 (31·8%)	20 523 (8·6%)
CovidLife (UK)	323 (3·2%)	18 195 (7·7%)
Gender		
Male	3202 (32·1%)	90 678 (38·2%)
Female	6772 (67·9%)	146 401 (61·7%)
Other	3 (<0·1%)	62 (<0·1%)
Data missing	2 (<0·1%)	129 (0·1%)
Age, years		
Mean age	46·6 (12·9)	48·9 (11·9)
18–29	1137 (11·4%)	13 084 (5·5%)
30–39	1701 (17·0%)	26 266 (11·1%)
40–49	3072 (30·8%)	100 097 (42·2%)
50–59	2512 (25·2%)	58 002 (24·4%)
60–69	656 (6·6%)	21 861 (9·2%)
≥70	435 (4·4%)	17 754 (7·5%)
Data missing	4 (<0·1%)	206 (0·1%)
Education		
Compulsory or less	286 (2·9%)	10 469 (4·4%)
Upper secondary, vocational, or other	2029 (20·3%)	60 679 (25·6%)
Bachelor's or diploma university degree	2507 (25·1%)	83 343 (35·1%)
Master's or PhD	1744 (17·5%)	47 786 (20·1%)
Data missing or not measured*	3413 (34·2%)	34 993 (14·7%)
Relationship status		
In a relationship	4356 (43·7%)	69 026 (29·1%)
Single	1501 (15·0%)	29 153 (12·3%)
Data missing or not measured†	4122 (41·3%)	138 691 (58·5%)
Body-mass index, kg/m²		
<25	4437 (44·5%)	77 587 (32·7%)
25–30	3246 (32·5%)	65 664 (27·7%)
>30	1764 (17·7%)	34 435 (14·5%)
Data missing or not measured	532 (5·3%)	59 584 (25·1%)
Current smoking		
Never	6018 (60·3%)	150 299 (63·3%)
Former smoker	2494 (25·0%)	27 537 (11·6%)
Current smoker	1198 (12·0%)	23 353 (9·8%)
Data missing	269 (2·7%)	36 081 (15·2%)
History of psychiatric disorders		
Yes	3110 (31·2%)	51 559 (21·7%)
No	6772 (67·9%)	180 200 (75·9%)
Data missing	97 (1·0%)	5511 (2·3%)

(Table continues on next page)

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.

Results

299 334 participants were included in the seven cohorts. After exclusion of participants with incomplete information on diagnosis of COVID-19 (n=41 346), main outcome measures of mental health symptoms (n=6103) and disease severity (n=448), and covariates (n=4188), the analytical cohort consisted of 247 249 individuals (appendix p 1). 9979 (4·0%) participants reported having tested positive for SARS-CoV-2 at some point during the study period, of whom 713 (7·1%) individuals were positive on an antibody test (table). Mean follow-up in the combined study sample was 5·65 months (SD 4·26; range 0–16), with mean follow-up of 10·30 months (1·69) in the longest follow-up category (>6 to 16 months; appendix p 3). The proportion of individuals with a COVID-19 diagnosis varied across cohorts (appendix pp 4–6) as did the cumulative prevalence of COVID-19 in each country during the study period (appendix p 7). A higher proportion of individuals with COVID-19 were female than male and they were on average younger than those not diagnosed with COVID-19 (table). Individuals diagnosed with COVID-19 had a higher educational level, were more likely to be in a relationship, to have lower body-mass index, have a history of smoking, and have chronic medical conditions, compared with individuals without a COVID-19 diagnosis (appendix pp 4–6). The overall prevalence of history of psychiatric disorders varied considerably between individuals with and without a COVID-19 diagnosis (table). EstBB-C19 and Omtanke2020 had the highest proportion of individuals with COVID-19 as well as the highest overall proportion of individuals with a previous diagnosis of psychiatric disorders (appendix pp 4–6). The absolute differences in history of psychiatric disorders between individuals with and without COVID-19 never exceeded 4% in any of the cohorts (appendix pp 4–6). Individuals who were bedridden for 7 days or longer represented 1613 (22·3%) of the 7226 patients with COVID-19 who had data on time spent bedridden (appendix pp 4–6).

Figure 1 (and appendix pp 8–21) shows PRs of adverse mental health symptoms among patients with COVID-19 0–16 months after diagnosis compared with individuals without such diagnosis, for each cohort and combined. The meta-analysis showed that compared with no previous COVID-19 diagnosis, previous COVID-19 diagnosis was associated with higher prevalence of symptoms of depression (multivariable adjusted PR 1·18

[95% CI 1·03–1·36], I^2 80·4%; p<0·0001) and poor sleep quality (1·13 [1·03–1·24], I^2 76·8%; p=0·0028) but not anxiety (0·97 [0·91–1·03], I^2 0·001%; p=0·56) or COVID-19-related distress (1·05 [0·93–1·20], I^2 73·7%; p=0·0034; figure 1). Estimates varied across all cohorts, especially for depression, for which results from EstBB-C19 differed substantially from other cohorts. When excluding EstBB-C19 from the depression analysis, the I^2 measure of heterogeneity was no longer statistically significant and the I^2 decreased by about 45% (I^2 34·7%; p=0·23). The analysis restricted to individuals (n=957) who responded to at least one questionnaire before and one after being diagnosed with COVID-19 (median time between responses: C19-Resilience, 7·3 months [IQR 6·9–7·9]; Omtanke2020, 1·1 months [1·0–1·2]; CovidLife, 10·0 months [9·0–10·0]) yielded similar PRs for depressive symptoms (PR 1·19 [95% CI 0·97–1·4]) and poor sleep quality (1·09 [0·88–1·35]; appendix p 22) after diagnosis of COVID-19, although with less precision than in the main analysis.

Longer time bedridden was consistently associated with increased PRs of all indicators of mental morbidities in a dose–response fashion (figure 2 and appendix pp 8–21). Compared with individuals never diagnosed with COVID-19, individuals who were never bedridden due to their SARS-CoV-2 infection had a significantly lower prevalence of symptoms of depression (PR 0·83 [95% CI 0·75–0·91]) and anxiety (0·77 [0·63–0·94]). Compared with individuals not diagnosed with COVID-19, individuals who were bedridden for 7 days or longer had a significantly higher prevalence of symptoms of depression (PR 1·61 [95% CI 1·27–2·05]), anxiety (1·43 [1·26–1·63]), and poor sleep quality (1·41 [1·24–1·61]), and a non-significantly higher prevalence of COVID-19-related distress (1·41 [0·96–2·06]; figure 2). Similarly, hospital admission was associated with increased PRs of all indicators of mental morbidities (appendix p 22).

Figure 3 (and appendix pp 8–21) shows the PRs of mental morbidities among individuals diagnosed with COVID-19 by months from diagnosis. Our analysis suggests some attenuation of symptoms of depression and a clear attenuation of COVID-19-related distress with time from diagnosis. The PR for depressive symptoms was 1·30 (95% CI 1·07–1·59) and for COVID-19-related distress was 1·20 (1·09–1·33) within 2 months after diagnosis but was not statistically significant beyond 2 months after diagnosis. These results were corroborated by estimates from the pair-wise comparison (appendix p 23). Compared with the first measurement after diagnosis, the last measurement among patients with COVID-19, mean 9·7 months (SD 2·8) later, yielded a lower prevalence of depressive symptoms (PR 0·88 [95% CI 0·76–1·01]; n=2883) and COVID-19-related distress (0·87 [0·75–1·00]; n=3846). The time-dependent pattern for symptoms of anxiety and poor sleep quality was less clear (appendix p 23).

	COVID-19 diagnosis (n=9979)	No COVID-19 diagnosis (n=237 270)
(Continued from previous page)		
Chronic medical conditions		
No condition	6567 (65·8%)	151 609 (63·9%)
One condition	2334 (23·4%)	47 194 (19·9%)
Two conditions	653 (6·5%)	14 090 (5·9%)
More than two conditions	220 (2·2%)	6902 (2·9%)
Data missing	205 (2·1%)	17 475 (7·4%)
Response periods		
March–June, 2020	1110 (11·1%)	179 891 (75·8%)
July–September, 2020	1801 (18·0%)	10 627 (4·5%)
October–December, 2020	3328 (33·4%)	39 592 (16·7%)
January–March, 2021	2184 (21·9%)	4760 (2·0%)
April–August, 2021	1556 (15·6%)	2400 (1·0%)
Illness severity: time bedridden‡		
Never bedridden	3160 (31·7%)	..
Bedridden 1–6 days	2453 (24·6%)	..
Bedridden 7 days or more	1613 (16·2%)	..
Data missing or not measured§	2753 (27·6%)	..
Illness severity: admitted to hospital		
Not admitted to hospital	8000 (80·2%)	..
Admitted to hospital	297 (3·0%)	..
Data missing or not measured¶	1682 (16·9%)	..
Time since diagnosis		
0 to 2 months	3108 (31·1%)	..
>2 to 6 months	3642 (36·5%)	..
>6 to 16 months	3229 (32·4%)	..

Data are n (%) or mean (SD). C19-Resilience=The Icelandic COVID-19 National Resilience Cohort. DBDS=The Danish Blood Donor Study. EstBB-C19=The Estonian Biobank COVID-19 Cohort. MAP-19=The Norwegian COVID-19, Mental Health and Adherence Project. MoBa=The Norwegian Mother, Father and Child Cohort Study. *Educational information not measured for Omtanke2020 (Sweden). †Relationship status not measured for EstBB-C19 (Estonia) and MoBa (Norway). ‡Time with fever for EstBB-C19 (no fever; fever for 1–6 days; fever for 7 days or more). §Illness severity: time bedridden not measured for MAP-19 (Norway) and CovidLife (UK). ¶Illness severity: admitted to hospital not measured for DBDS (Denmark) and MAP-19 (Norway).

Table: **Baseline characteristics**

Figure 4 (and appendix pp 23–24) shows mental health symptom development during the first 16 months after COVID-19 diagnosis by time bedridden in the acute illness. Although we found that mental health symptoms overall attenuated with time from COVID-19 diagnosis, patients bedridden for 7 days or longer, compared with participants without a COVID-19 diagnosis, showed persistent symptoms of depression (PR 1·66 [95% CI 1·11–2·47] at 0 to 2 months after diagnosis; 1·53 [1·26–1·86] at more than 2 months to 6 months after diagnosis; and 1·60 [1·17–2·81] at more than 6 months to 16 months after diagnosis), anxiety (PR 1·47 [95% CI 0·80–2·72] at 0 to 2 months after diagnosis; 1·46 [1·20–1·79] at more than 2 months to 6 months after diagnosis; and 1·47 [1·19–1·81] at more than 6 months to 16 months after diagnosis), and poor sleep quality (PR 1·35 [95% CI 1·11–1·64] at 0 to 2 months after diagnosis; 1·48 [1·29–1·69] at more than

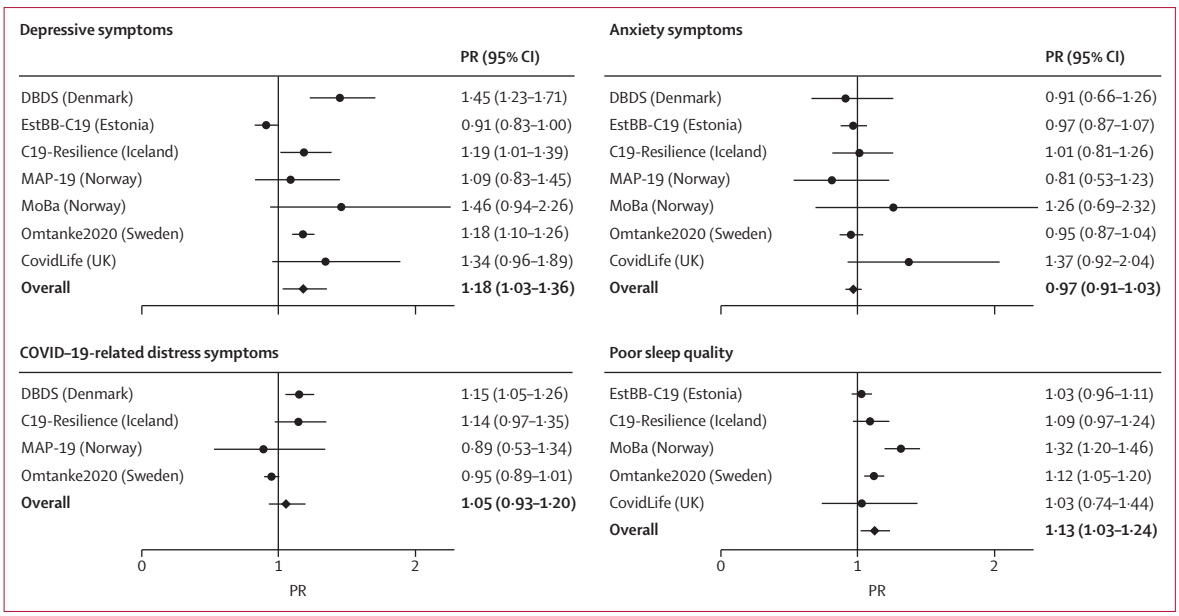

Figure 1: **Mental health indicators among individuals with a diagnosis of COVID-19 compared with individuals without a COVID-19 diagnosis**
C19-Resilience=The Icelandic COVID-19 National Resilience Cohort. DBDS=The Danish Blood Donor Study. EstBB-C19=The Estonian Biobank COVID-19 Cohort. MAP-19=The Norwegian COVID-19, Mental Health and Adherence Project. MoBa=The Norwegian Mother, Father and Child Cohort Study. PR=prevalence ratio.

2 months to 6 months after diagnosis; and 1·26 [0·90–1·77] at more than 6 months to 16 months after diagnosis). By contrast, we observed a clear attenuation of COVID-19-related distress symptoms among patients with COVID-19 who were bedridden for 7 days or more (PR 1·78 [95% CI 1·29–2·46] at 0 to 2 months after diagnosis; 1·17 [0·93–1·47] at more than 2 to 6 months after diagnosis; and 1·01 [0·52–1·96] at more than 6 to 16 months after diagnosis). Patients never bedridden due to COVID-19 showed the opposite pattern of lower PRs of depression, anxiety, and COVID-19-related distress symptoms compared with participants with no COVID-19 diagnosis.

Discussion

In this multicohort study including almost 250 000 individuals across six countries, we found that acute COVID-19 illness severity was associated with mental morbidities up to 16 months after diagnosis. Although individuals who were never bedridden due to COVID-19 had lower risks of adverse mental health symptoms compared with those not diagnosed with COVID-19, individuals who were bedridden for 7 days or longer—representing 22·3% of the participants with a COVID-19 diagnosis—persistently showed 50–60% higher prevalence of depression and anxiety symptoms throughout the observation period.

To our knowledge, our study is the first to report disease severity as an important modifier of long-term mental health among individuals with a COVID-19 diagnosis in the general population across six countries. Our findings are in line with the limited existing literature on both inpatients and outpatients, indicating a link between COVID-19 diagnosis and mental health status.[1–3,32] However, the longest follow-up in these studies was 6 months, except for one recent study with 1-year follow-up involving only patients admitted to hospital. In that study, 331 (26%) of 1271 patients with COVID-19 had anxiety or depression at 12-month follow-up,[32] which is similar to the results of our study. In previous outbreaks of other infectious diseases, a high prevalence of post-traumatic stress disorder and depressive disorders have been observed after diagnosis. For example, a high prevalence of these symptoms was observed up to 4 years after diagnosis of severe acute respiratory syndrome in 2003[33] and these symptoms were also reported following the 2015 outbreak of Middle East respiratory syndrome up to 12 months after diagnosis.[34] However, disease severity was generally not addressed in these studies, which also were limited to patients admitted to hospital.[34] Collectively, the existing literature suggests that the elevated relative risks of mental morbidities are not limited to COVID-19 but have also been reported after other previous pandemic infections.

Our findings suggest that almost a quarter of patients with a COVID-19 diagnosis had symptoms severe enough for them to be bedridden for 7 days or longer, which was associated with persistent long-term mental health symptoms.[35] Our study participants were diagnosed with COVID-19 from February, 2020, to August, 2021; therefore, with the advent of vaccinations and new, reportedly weaker SARS-CoV-2 variants,[35] the proportion of patients with COVID-19 with a severe course of acute illness might be lower in more recently infected individuals.

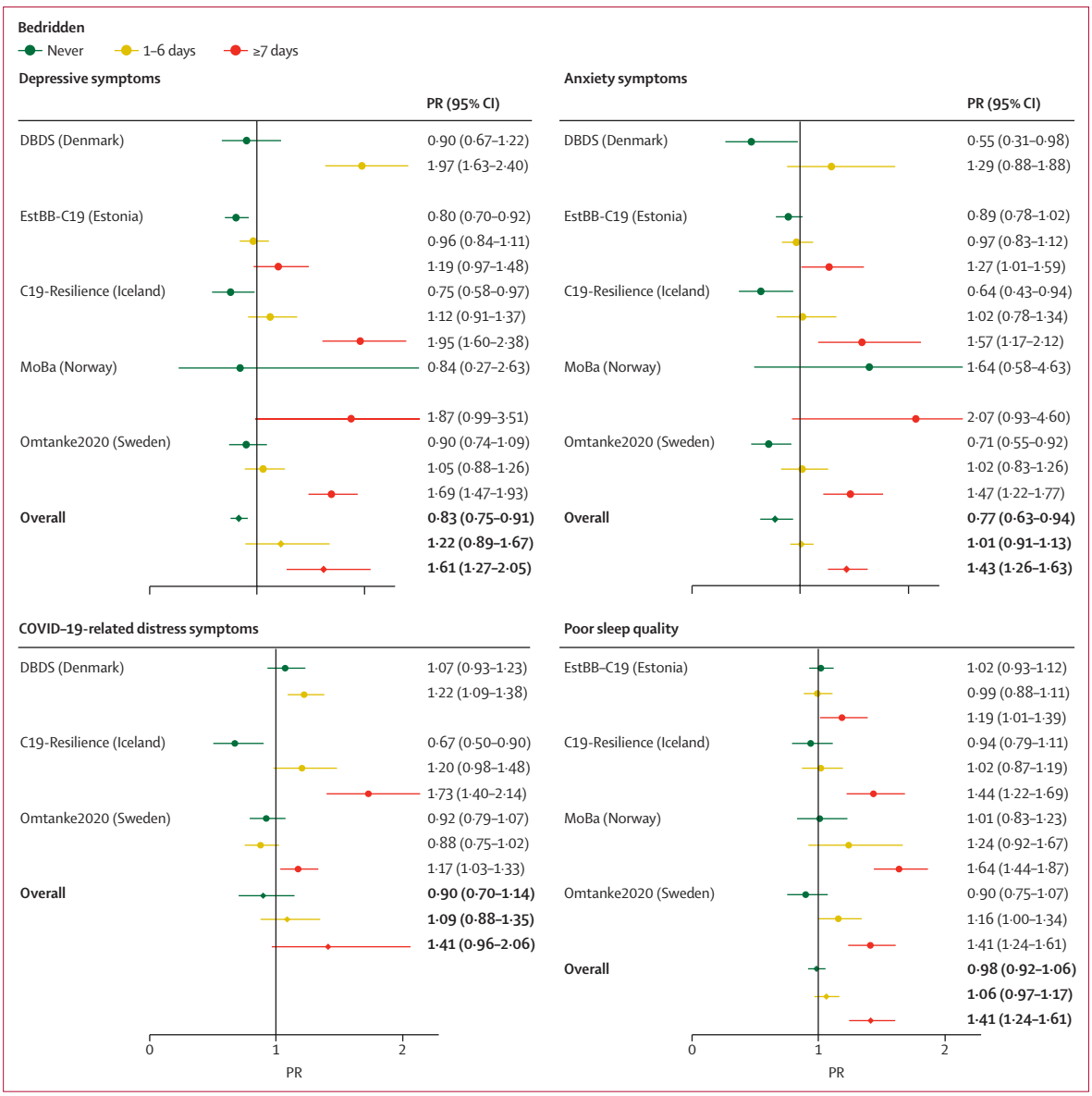

Figure 2: **Mental health indicators among individuals with a diagnosis of COVID-19 compared with individuals without a COVID-19 diagnosis by illness severity (time bedridden)**

C19-Resilience=The Icelandic COVID-19 National Resilience Cohort. DBDS=The Danish Blood Donor Study. EstBB-C19=The Estonian Biobank COVID-19 Cohort. MAP-19=The Norwegian COVID-19, Mental Health and Adherence Project. MoBa=The Norwegian Mother, Father and Child Cohort Study. PR=prevalence ratio.

The persistent elevated symptom levels of depression and anxiety among patients with COVID-19 who were bedridden for 7 days or longer could be due to several mechanisms. This could include the worry of having infected others[9] and the unpredictable prognosis of COVID-19 (eg, worrying about long-term health effects, or even death[8]). However, such psychological mechanisms might be expected to lead to transient mental health symptoms that attenuate with time (ie, with recovery of physical symptoms of the illness). Indeed, the observed increase in symptoms of COVID-19-related distress in this group of patients might be indicative of such psychological mechanisms as the symptoms attenuated quickly after 2 months of diagnosis. By contrast, the persistent symptoms of depression and anxiety among individuals who were bedridden for 7 days or longer might be due to continued physical long COVID symptoms where functional limitations, perhaps limiting social contact, might cause worry and a sense of helplessness.[13] Alternatively, the inflammatory processes among patients with severe acute illness could also affect the risk of persistent mental health symptoms.[4,11] Indeed, inflammation associated with chronic[36] and infectious[37] diseases have previously been linked with development

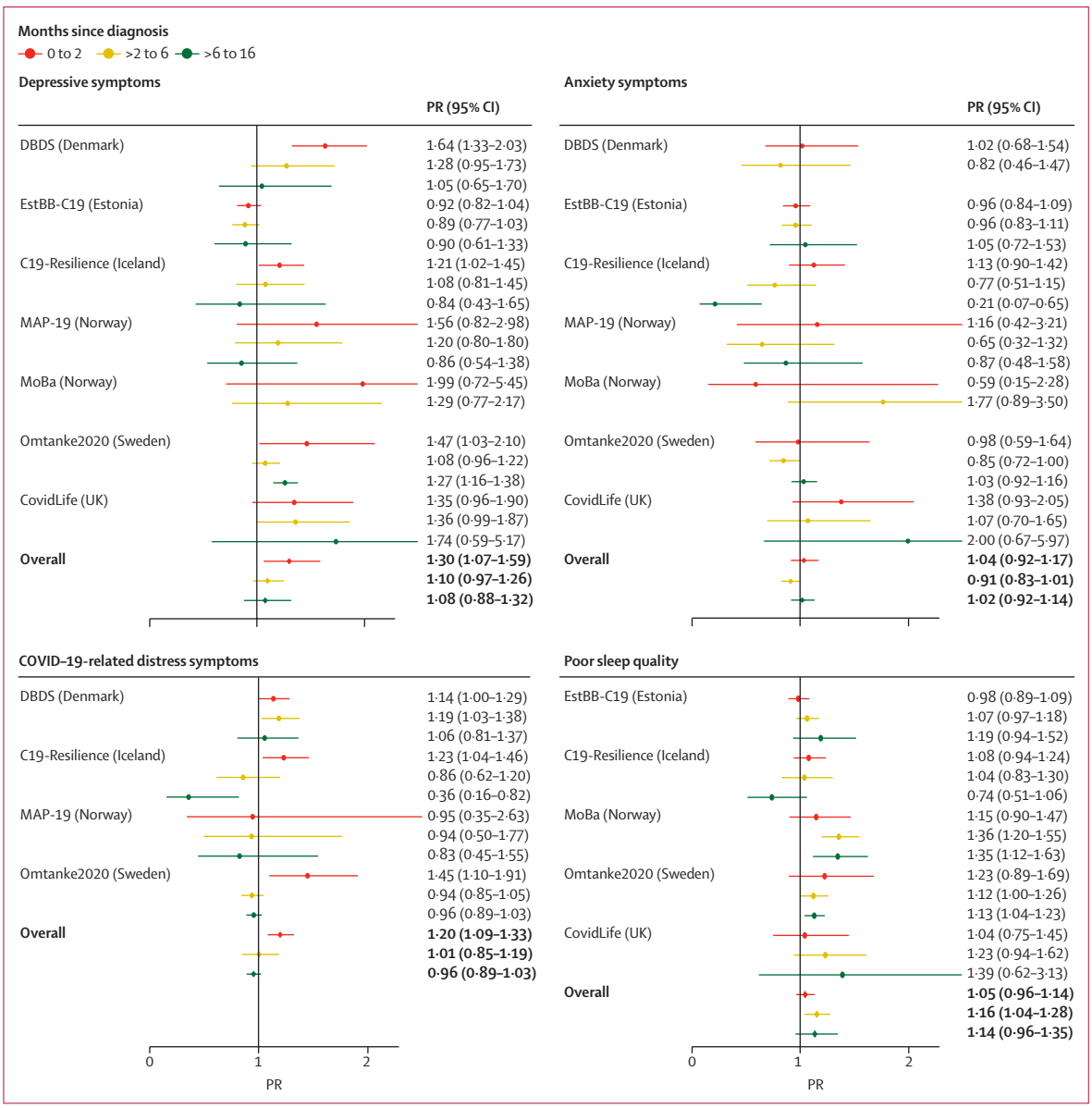

Figure 3: **Mental health indicators among individuals with a diagnosis of COVID-19 compared with individuals without COVID-19 by time since diagnosis**
C19-Resilience=The Icelandic COVID-19 National Resilience Cohort. DBDS=The Danish Blood Donor Study. EstBB-C19=The Estonian Biobank COVID-19 Cohort. MAP-19=The Norwegian COVID-19, Mental Health and Adherence Project. MoBa=The Norwegian Mother, Father and Child Cohort Study. PR=prevalence ratio.

of mental morbidities, particularly depression. Such mental morbidities have also been reported to persist after reduction in inflammation.[38] Hospital admission represents another severity indicator of acute COVID-19 illness in our study; whether the high prevalence of depression in this group is mediated by aforementioned inflammatory processes, social isolation, or both, remains to be further elucidated.

By contrast, we found that a mild course of acute illness (ie, never bedridden) was associated with a persistently lower risk of adverse mental health outcomes throughout the follow-up period. Several factors might contribute to this pattern. For example, individuals with a mild COVID-19 infection were able to return to somewhat more normal lives after the benign infection as compared with their more severely impacted counterparts who still could be restrained by fear of ongoing symptoms. Also, the extended duration of official gathering restrictions might have had less impact on the mental health of recovered asymptomatic COVID-19 patients than the general population, as they could, for example, visit relatives without the fear of infecting them. It is also possible that individuals with a low risk of mental morbidities before the pandemic had a less severe

disease course after being infected with SARS-CoV-2, yielding the observed associations. Indeed, individuals with a history of psychiatric disorders have been reported to be at increased risk of being diagnosed with COVID-19 as well as risk of adverse COVID-19 outcomes.[12] In the current study, the prevalence of psychiatric disorders was slightly higher among individuals with COVID-19 than those without a diagnosis; thus we included this variable in all our regression models, and when considering the association between time bedridden during the acute illness and symptoms of long-term mental morbidities. Nevertheless, we cannot exclude the possibility of residual confounding—ie, that previous psychiatric vulnerabilities lead to more severe acute COVID-19, yielding the observed associations in our data. This potentially bidirectional association between psychiatric morbidity and COVID-19 requires further study through prospective designs.

The strengths of our study include the almost 10 000 individuals from the general population of six European countries who self-reported a confirmed diagnosis of COVID-19 of varying disease severities (ranging from virtually no COVID-19 symptoms to intensive care unit admission) and the large comparison group without a COVID-19 diagnosis. Although many previous large studies are based on electronic health records, our study leveraged prospective data collections with validated measures of mental health indicators along with the extended spectra of considered covariates to diminish risks related to measurement bias and confounding. The limitations of our study include the self-reports of COVID-19 diagnosis and mental morbidities that are all to some extent inter-related and cannot be viewed as four independent phenotypes. Moreover, there were considerable differences in response periods of individuals with and without COVID-19. More than 75% of the comparison group responded between March and June, 2020, when there was still great fear and uncertainty about the implications of the disease, whereas responses of patients with COVID-19 accumulated from March, 2020, until August, 2021. However, the response periods were included in the multivariable models and should therefore not explain our findings completely. Individuals diagnosed with COVID-19 were on average younger than those not diagnosed with the disease, indicating that we might have missed some older patients with COVID-19, particularly those who had a severe disease course. If true, such selection would yield attenuated estimates of mental morbidity in the COVID-19 group. Another possible weakness pertains to the different recruitment strategies of the included cohorts, which could explain the somewhat varying cohort-specific results for some of the mental health outcomes. Some national cohorts specifically targeted individuals tested for or diagnosed with COVID-19 in their recruitment (ie, EstBB-C19 and C19-Resilience), whereas others did not. Yet, 4·0% of the total multinational cohort reported a confirmed diagnosis of COVID-19, which is in line with the prevalence in four of the six countries included in this study during the study period (appendix p 7). The prevalence ratios were somewhat similar across cohorts, independent of recruitment strategies, suggesting an absence of substantial systematic bias. Finally, the exposed population of our study is limited to individuals who tested positive for SARS-CoV-2 infection; we have no information on infected individuals who were not tested for SARS-CoV-2.

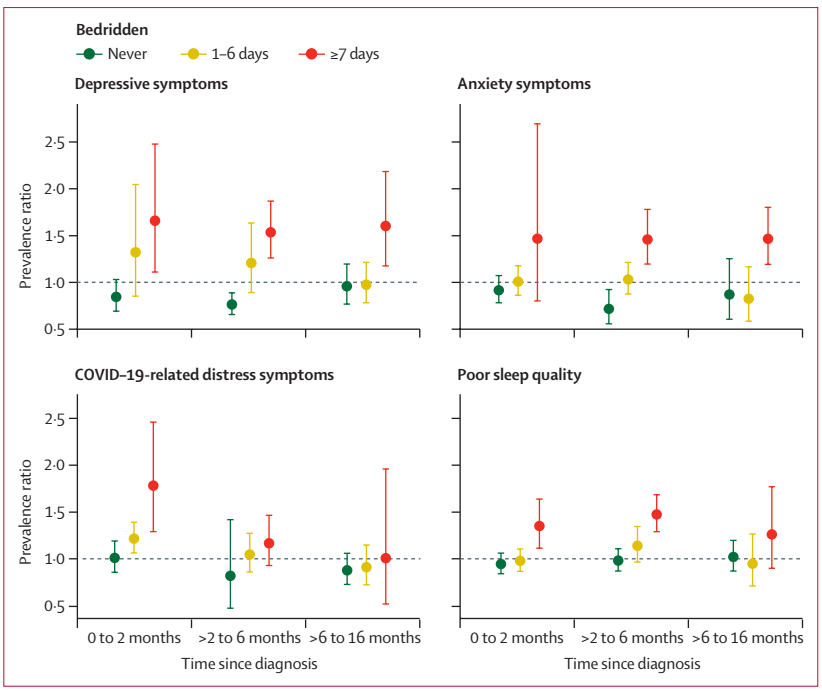

Figure 4: **Mental health indicators during the first 16 months after diagnosis of COVID-19 by time bedridden**

In conclusion, in this study we found that severe COVID-19 acute illness was associated with long-term mental health symptomology among recovered patients. Although patients with mild acute COVID-19 illness are unlikely to have long-term mental health morbidities, more than a fifth of the included patients with COVID-19 had a severe acute illness course (the large majority at home, although some in hospital), which was associated with persistent risks of depressive and anxiety symptoms up to 16 months after diagnosis. These findings motivate continued clinical vigilance and follow-up studies beyond the first year among individuals with the most severe symptomology after COVID-19 infections.

COVIDMENT Collaboration
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Contributors

The COVIDMENT cohorts and their data collections were designed by IM, AL, ABU, CF-R, HA, KK, LANC, SUJ, OVE, AHo, DJP, FF, JJ, KL, OAA, OBVP, TA, UAV, and their respective teams. UAV, IM, and TA directed the combined effort of this study implementation. UAV, IM, JJ, and TA designed the analytical strategy in close collaboration with all team members and all authors helped to interpret the findings. IM, AL, ABU, DM, HA, KK, LANC, and SUJ conducted the literature review and drafted the manuscript under the supervision of UAV. All authors revised the manuscript for critical content and approved the final version of the manuscript. IM and TA had access to and verified all the data and all authors could access the data on request.

Declaration of interests

OAA has received a grant to their institution from Nordforsk and Research Council of Norway for the present manuscript. OAA has also received a grant to the institution for an entity other than the present manuscript from South East Norway Health Authority, KG Jebsen Stiftelsen, and National Institutes of Health, EU. OAA has received royalties for a textbook in psychiatry, consulting fees from HealthLytix and Milken Institute, payment for lectures from Sunovion and Lundbeck, and payment for expert testimony from the Norwegian Court. Outside of this work, OAA has a patent for a devise for nasal delivery. OAA has participated at his institution on boards for local principal investigator Clinical Trial Janssen, local principal investigator Clinical Trial MAPS, and local principal investigator Clinical Trial Boehringer. UAV has received grants for the current work from Nordforsk and Horizon2020 as well as grants outside the current work from the Icelandic Research Fund, Swedish Research Council, Swedish Cancer Society, and the European Research Council. All other authors declare no competing interests.

Data sharing

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.

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