Depression, worry, and loneliness are associated with subsequent risk of hospitalization for COVID-19: a prospective study

Original Article

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Abstract

Background. Pre-pandemic psychological distress is associated with increased susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, but associations with the coronavirus disease 2019 (COVID-19) severity are not established. The authors examined the associations between distress prior to SARS-CoV-2 infection and subsequent risk of hospitalization.

Methods. Between April 2020 (baseline) and April 2021, we followed 54 781 participants from three ongoing cohorts: Nurses' Health Study II (NHSII), Nurses' Health Study 3 (NHS3), and the Growing Up Today Study (GUTS) who reported no current or prior SARS-CoV-2 infection at baseline. Chronic depression was assessed during 2010–2019. Depression, anxiety, worry about COVID-19, perceived stress, and loneliness were measured at baseline. SARS-CoV-2 infection and hospitalization due to COVID-19 was self-reported. Relative risks (RRs) were calculated by Poisson regression.

Results. 3663 participants reported a positive SARS-CoV-2 test (mean age = 55.0 years, standard deviation = 13.8) during follow-up. Among these participants, chronic depression prior to the pandemic [RR = 1.72; 95% confidence interval (CI) 1.20–2.46], and probable depression (RR = 1.81, 95% CI 1.08–3.03), being very worried about COVID-19 (RR = 1.79; 95% CI 1.12–2.86), and loneliness (RR = 1.81, 95% CI 1.02–3.20) reported at baseline were each associated with subsequent COVID-19 hospitalization, adjusting for demographic factors and healthcare worker status. Anxiety and perceived stress were not associated with hospitalization. Depression, worry about COVID-19, and loneliness were as strongly associated with hospitalization as were high cholesterol and hypertension, established risk factors for COVID-19 severity.

Conclusions. Psychological distress may be a risk factor for hospitalization in patients with SARS-CoV-2 infection. Assessment of psychological distress may identify patients at greater risk of hospitalization. Future work should examine whether addressing distress improves physical health outcomes.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has led to over 4.4 million hospital admissions in the United States (CDC, 2022), severely straining healthcare systems (Grimm, 2021). Identified risk factors for hospitalization due to severe coronavirus disease 2019 (COVID-19) include age, obesity, asthma, hypertension, and diabetes (Garg et al., 2020), in addition to behaviors such as smoking (Hamer, Kivimäki, Gale, & Batty, 2020). Various forms of distress, including depression, anxiety, and perceived stress, have also been implicated in elevated susceptibility to infections, including SARS-CoV-2 (Batty et al., 2020; Orlando et al., 2021; Taquet, Luciano, Geddes, & Harrison, 2021; Yang et al., 2020a), as well as increased severity of infectious disease (Aiello, Simanek, Stebbins, & Dowd, 2018; Cohen et al., 1995; Falagas, Karamanidou, Kastoris, Karlis, & Rafailidis, 2010; Janicki Deverts, Cohen, & Doyle, 2017). Numerous prospective studies have additionally identified loneliness (LeRoy, Murdock, Jaremka, Loya, & Fagundes, 2017) and other factors associated with distress (e.g. small social network, low emotional support) (Cohen, Doyle, Skoner,

Rabin, & Gwaltney, 1997; Cohen, Doyle, Turner, Alper, & Skoner, 2003) as potential contributors to a worse course of respiratory infections, although not consistently (Bu, Philip, & Fancourt, 2020; Hamrick, Cohen, & Rodriguez, 2002).

Better understanding of the links between psychological distress and risk of COVID-19-hospitalization may help prevent severe outcomes and strain on healthcare systems by identifying those at greatest risk. Although the Centers for Disease Control and Prevention have identified mental health conditions as risk factors for COVID-19 severity (People with Certain Medical Conditions, 2021), our understanding of the association of distress with COVID-19 severity remains incomplete. Prior studies have primarily investigated mortality as the outcome (Lee et al., 2020; Li, Li, Fortunati, & Krystal, 2020; Nemani et al., 2021; Wang, Xu, & Volkow, 2021), leaving the association with hospitalization comparatively unexplored. Most studies used medical records of mental illness diagnoses to measure psychological distress (Lee et al., 2020; Li et al., 2020; Nemani et al., 2021; Orlando et al., 2021; Taquet et al., 2021; Wang et al., 2021; Yang et al., 2020a). However, medical records have only moderate sensitivity to detect common mental disorders such as depression and anxiety (Beesley et al., 2020; Spiranovic, Matthews, Scanlan, & Kirkby, 2016; Townsend, Walkup, Crystal, & Olfson, 2012), which are frequently undiagnosed (Gwynn et al., 2008; Ko, Farr, Dietz, & Robbins, 2012; Perruche et al., 2011). Additionally, some medical record studies examined the diagnosis of any psychiatric disorder as a single exposure, reducing the utility for intervention and prediction (Li et al., 2020; Wang et al., 2021). No studies have examined other common manifestations of distress, such as perceived stress and loneliness in relation to hospitalization from COVID-19.

In the present study, we prospectively examined whether various manifestations of psychological distress prior to infection with SARS-CoV-2 predicted hospitalization among individuals after SARS-CoV-2 infection, using data from three large longitudinal cohorts: the Nurses' Health Study II (NHSII), the Nurses' Health Study III (NHS3), and the Growing Up Today Study (GUTS) (Bao et al., 2016). We additionally examined the extent to which established risk factors for COVID-19 hospitalization (e.g. age, diabetes, asthma, hypertension, smoking, obesity) accounted for possible associations.

Methods

Study design and population

Study participants were drawn from the Nurses Health cohorts, a set of cohorts initiated in the early 1970s to study the long-term health effects of exogenous hormone use in the early 1970s in a medically sophisticated group. The NHSII is a cohort of 116 429 female registered nurses living in the US, enrolled in 1989 at ages of 25–42 years and followed biennially. The NHSII was established to study the health effects of oral contraceptive use and other health risk factors among women of reproductive age. The NHS3, currently recruiting, was established in 2010 and includes more than 40 000 female nurses aged 18 years and older, living in the US or Canada and followed biannually using web-based questionnaires. NHS3 recruited more participants of different race/ethnicity groups. Recruitment was extended to male nurses in 2015 ($N = 856$). GUTS began in 1996 when NHSII participants enrolled their offspring ($N = 27\,793$) aged 9–17 years to study the potential impacts of factors (e.g. diet and exercise) that influence weight change trajectory throughout the life course.

From April 2020 to May 2020, we invited participants who returned the most recent main cohort questionnaire to complete a supplementary online COVID-19 survey. Of 105 662 invited participants, 58 612 (55%) responded to the first COVID-19 questionnaire from April 2020 to August 2020 (termed 'baseline' henceforth). Respondents were then administered monthly surveys. Additional weekly surveys were administered to those who self-identified as frontline healthcare workers ($n = 23\,053$). In August 2020, the surveys changed to quarterly administration (online Supplementary Figs S1 and S2). The end of follow-up for the current analysis was 27 April 2021. Among 58 612 people who responded to the COVID-19 baseline survey, we further restricted the analysis to 54 781 participants with no documented history of SARS-CoV-2 infection and not hospitalized at baseline who returned at least one follow-up questionnaire.

The study was approved by the Partners Healthcare System Institutional Review Board. Return of questionnaires constituted implied consent.

Measures

Forms of distress

Chronic depression in the 10 years prior to the COVID-19 pandemic was derived from multiple indicators queried at varying intervals on main cohort questionnaires, 2010–2019. These included self-reported physician-diagnosed depression, use of antidepressants, and depressive symptoms as reported on the Center for Epidemiologic Studies Depression Scale-10 (CESD-10) and the Patient Health Questionnaire-9 (PHQ-9) (online Supplementary Table S1). Participants were considered to have a history of chronic depression if they reported any indicator of depression at two or more time points.

All other forms of distress were assessed at the COVID-19 study baseline. Current depression and anxiety symptoms were assessed with the PHQ-4, which combines a 2-item measure of depression (PHQ-2) and a 2-item measure of anxiety [Generalized Anxiety Disorder-2 (GAD-2)] (Kroenke, Spitzer, Williams, & Lowe, 2009). The PHQ-4 queries frequency of symptoms, with response options 0 ('not at all') to 3 ('nearly every day'). A summed score of 3 or greater on each subscale indicates probable major depressive disorder or anxiety disorder (Kroenke, Spitzer, & Williams, 2003; Kroenke, Spitzer, Williams, Monahan, & Lowe, 2007). To create reference groups with no symptoms, and to examine possible dose-dependent relations, we divided these scores into three levels for analysis: 0 points (reference), 1–2 points (subclinical symptoms), ⩾3 points (probable depression or anxiety). The PHQ-2 and GAD-2 have been validated against clinical diagnosis (Kroenke et al., 2003, 2007, 2009; Lowe et al., 2010). Worry about COVID-19 was assessed with a single question, 'How worried are you about COVID-19?' with response options: 'not at all', 'not very', 'somewhat', and 'very worried' (YouGov, 2020). 'Not at all' and 'not very worried' were combined to serve as the reference group, as only 5.9% participants responded 'not at all worried'.

Due to concerns about participant burden, two additional forms of distress were assessed only among non-healthcare workers. The 4-item Perceived Stress Scale (PSS-4) (Cohen, 1988), a shortened version of the well-validated 14-item PSS (Cohen, Kamarck, & Mermelstein, 1983), assesses the ability to cope with existing stressors. Total scores range from 0 to 16,

with higher scores indicating higher levels of perceived stress, with satisfactory psychometrics (Cohen, 1988; Mitchell, Crane, & Kim, 2008; Vallejo, Vallejo-Slocker, Fernandez-Abascal, & Mananes, 2018; Warttig, Forshaw, South, & White, 2013). Loneliness was assessed with the 3-item UCLA Loneliness Scale (Hughes, Waite, Hawkley, & Cacioppo, 2004) which has demonstrated good internal consistency reliability and validity (Hughes et al., 2004; Steptoe, Shankar, Demakakos, & Wardle, 2013). Participants reported how often they felt: (i) lack of companionship; (ii) left out; and (iii) isolated from others. Responses were coded as 1 ('hardly ever'), 2 ('some of the time'), and 3 ('often'), with higher scores indicating greater loneliness. We divided the score into three levels for analysis, 3 points (loneliness hardly ever, reference), 3–5 points (less than some of the time), and ⩾6 points (some of the time or often) (Steptoe et al., 2013). For all continuous scores, effects associated with an increase of one interquartile range (IQR) were estimated. Because the distribution of the scores were skewed, IQRs were approximate.

COVID-19 infection and hospitalization

Past 7-, 30-, and 90-day positive SARS-CoV-2 diagnostic test (antibody, antigen, or PCR), COVID-19 symptoms, and hospitalization due to COVID-19 occurring since 1 March 2020, were self-reported on all questionnaires. Participants were asked specifically, 'Have you been hospitalized because of COVID-19?' and the treatments they received, including intravenous fluid, oxygen through nasal prong or facial mask, ICU admission, and invasive ventilation.

Covariates

All covariates were assessed prior to the pandemic in main cohort questionnaires, using the most recent data available (online Supplementary Table S2). Demographic factors included age, race/ethnic identity, sex, and educational attainment of the participant (GUTS) or their spouse/partner (NHSII and NHS3). Risk factors for COVID-19 severity included body mass index (BMI), smoking, and history of clinician-diagnosed: diabetes, hypertension, high cholesterol, asthma, and cancer (yes/no for each of the diseases).

Statistical analysis

To examine the association of distress and risk of SARS-CoV-2 infection, we compared level of distress among participants with and without a positive SARS-CoV-2 diagnostic test during follow-up. Among participants who reported a positive SARS-CoV-2 test, we compared the prevalence of established risk factors for severe COVID-19 and demographic factors by forms of distress at baseline. To examine the association of distress with risk of subsequent hospitalization for COVID-19, we fit Poisson regression models with hospitalization as the dependent variable with each form of distress as the independent variable in separate models adjusted for demographic factors, educational attainment, and healthcare worker status. To examine whether health risk factors that commonly co-occur with distress might account for possible associations, we further adjusted for: (1) health behavioral factors including BMI and smoking; and (2) health behavioral factors and history of hypertension, diabetes, high cholesterol, asthma, and cancer.

We conducted several sensitivity analyses. First, as frontline healthcare workers have higher risk of infection and increased psychological distress than non-healthcare workers (Chou et al., 2020; Preti et al., 2020; Sasaki, Kuroda, Tsuno, & Kawakami, 2020; Zheng et al., 2020), we investigated the association of forms of distress with COVID-19 hospitalization stratified by healthcare worker status and tested a distress-by-healthcare-worker-status interaction term. Second, we further adjusted for month using indicator variables, to account for the different phases of the pandemic. Third, although we excluded participants who reported a positive SARS-CoV-2 test at baseline, some participants reported COVID-19-related symptoms at baseline. Therefore, to ensure that distress preceded SARS-COV-2 infection, we further excluded 175 respondents who were identified as possible cases using a symptom-based predictor of SARS-CoV-2 infection (Rich-Edwards et al., 2021). Fourth, we excluded 104 participants who reported a positive SARS-COV-2 test within 30 days of return of the baseline questionnaire, to minimize the possibility that prodromal symptoms were causing psychological distress. Fifth, to remove possible effects of vaccination on SARS-CoV-2 susceptibility and severity, we excluded people who reported SARS-COV-2 infections after participants could have been fully vaccinated (1 February 2021 for active healthcare workers, *N* excluded = 225, and 1 April 2021 for non-healthcare workers, *N* excluded = 21). Sixth, we further adjusted for cohort and number of questionnaires. Seventh, to examine the possible difference in sex, we stratified the analysis by sex. As only 1 male participant was hospitalized, models restricted to males did not convergence. We presented analyses to female participants (*n* = 3535). Eighth, we fit models using the most recent measures of pre-infection psychological distress as independent variables. Ninth, to evaluate whether loneliness might be a proxy for low availability of getting care when sick, we adjusted for the living situation reported at baseline (living alone or not).

For all models, relative risks (RRs) were estimated using generalized linear models (Zou, 2004) in SAS 9.4 (SAS Institute). A 2-sided *p* < 0.05 was considered statistically significant.

Results

The 54 781 participants who returned at least one follow-up questionnaire were primarily female (96.6%) and White (96.5%), with mean age = 57.5 years (s.d. = 13.8). More than one third of participants (38.0%) were frontline healthcare workers. We documented 3663 incident cases of SARS-CoV-2 (6.7% of participants) from 1 May 2020, to 1 April 2021. At baseline, the mean age of participants who had a positive SARS-CoV-2 test during follow-up was 55.0 years (s.d. = 13.8); 96.5% were female, 128 (3.5%) were male, 96.7% were White, and 52.1% were frontline healthcare workers. The mean (s.d.) age of male participants was 33.4 (4.9). 34 (26.6%) of male participants were active healthcare workers. The median time from return of baseline questionnaire to positive SARS-CoV-2 test was 30 weeks (range, 1–47 weeks). Active healthcare workers had elevated level of depression and anxiety at baseline compared to non-active healthcare workers (depressive symptoms: 1.18 *v.* 1.06; anxiety symptoms: 1.60 *v.* 1.35). The prevalence of all forms of distress at baseline was similar among respondents who reported a positive SARS-CoV-2 test during follow up and those who did not (online Supplementary Table S3).

Respondents with probable depression or anxiety at baseline were younger, had higher BMI, had a higher prevalence of asthma, and were more likely to be frontline healthcare workers than those who had no symptoms of these disorders (Table 1). Compared with participants who reported not being worried or

Table 1. Health and demographic characteristics by forms of distress at baseline (April–August 2020), among participants who ever tested positive for SARS-CoV-2 between April 2020 – April 2021, N = 3663

		Depressive symptoms		Anxiety symptoms		Worry about COVID-19		Loneliness	
		No symptoms	Probable depression	No symptoms	Probable anxiety	No	High	Hardly ever	Yes
		N = 1790	N = 477	N = 1349	N = 767	N = 1105	N = 597	N = 748	N = 501
Age, years	mean (s.d.)	57.4 (12.8)	49.9 (14.6)	59.4 (12.0)	50.2 (14.3)	56.4 (13.6)	55.3 (13.7)	57.7 (14.5)	56.8 (15.1)
Race									
White		1737 (97.0)	462 (96.9)	1304 (96.7)	744 (97.0)	1080 (97.7)	566 (94.8)	730 (97.6)	490 (97.6)
Sex									
Female	N (%)	1727 (96.5)	460 (96.4)	1297 (96.2)	743 (96.9)	1049 (94.9)	587 (98.3)	704 (94.1)	473 (94.4)
Male	N (%)	63 (3.5)	17 (3.6)	52 (3.9)	24 (3.1)	56 (5.1)	10 (1.7)	44 (5.9)	28 (5.6)
Frontline healthcare worker, yes	N (%)	892 (49.8)	284 (59.5)	605 (44.9)	449 (58.5)	504 (45.6)	310 (51.9)	–	–
Partner's education[b]									
High school or lower	N (%)	227 (12.7)	40 (8.4)	204 (15.1)	61 (8.0)	138 (12.5)	56 (9.4)	92 (12.3)	49 (9.8)
College	N (%)	732 (40.9)	146 (30.6)	525 (38.9)	275 (35.9)	450 (40.7)	187 (31.3)	286 (38.2)	171 (34.1)
Graduate school	N (%)	300 (46.8)	76 (15.9)	228 (16.9)	130 (17.0)	178 (16.1)	103 (17.3)	137 (18.3)	77 (15.4)
Unmarried	N (%)	471 (26.3)	200 (41.9)	343 (25.4)	278 (36.3)	303 (27.4)	229 (38.4)	194 (25.9)	184 (36.7)
BMI, kg/m^2									
<18.5	N (%)	25 (1.4)	5 (1.1)	17 (1.3)	8 (1.0)	19 (1.7)	8 (1.3)	9 (1.2)	9 (1.8)
18.5 to <25	N (%)	607 (33.9)	123 (25.8)	427 (31.7)	225 (29.3)	379 (34.3)	162 (27.1)	235 (31.4)	141 (28.1)
25 to <30	N (%)	526 (29.4)	123 (25.8)	412 (30.5)	222 (28.9)	335 (30.3)	170 (28.5)	221 (29.6)	136 (27.2)
30 to <35	N (%)	346 (19.3)	86 (18.0)	282 (20.9)	127 (16.6)	199 (18.0)	94 (15.8)	122 (16.3)	98 (19.6)
⩾35	N (%)	221 (12.6)	98 (20.6)	172 (12.8)	136 (17.7)	127 (11.5)	126 (21.1)	116 (15.5)	87 (17.4)
Smoking status									
Current	N (%)	44 (2.5)	18 (3.8)	40 (3.0)	25 (3.3)	30 (2.7)	22 (3.7)	17 (2.3)	16 (3.2)
Former	N (%)	449 (25.1)	113 (23.7)	388 (28.8)	178 (23.4)	269 (24.3)	181 (30.3)	180 (24.1)	125 (25.0)
Never	N (%)	1297 (72.5)	346 (72.5)	921 (68.3)	564 (73.5)	808 (72.9)	394 (66.0)	551 (73.7)	360 (71.9)
Diabetes, ever	N (%)	94 (5.3)	23 (4.8)	83 (6.2)	35 (4.6)	55 (5.0)	32 (5.4)	46 (6.2)	36 (7.2)
Hypertension, ever	N (%)	354 (39.8)	100 (21.0)	296 (21.9)	157 (20.5)	224 (20.3)	146 (24.5)	182 (24.3)	133 (26.6)
High cholesterol, ever	N (%)	439 (24.5)	125 (26.2)	355 (26.3)	194 (25.3)	286 (25.9)	165 (27.6)	202 (27.0)	147 (29.3)
Asthma, ever	N (%)	196 (11.0)	103 (21.6)	126 (9.3)	145 (18.9)	119 (10.8)	97 (16.3)	89 (11.9)	70 (14.0)
Cancer, ever	N (%)	88 (4.9)	23 (4.8)	68 (5.0)	33 (4.3)	51 (4.6)	33 (5.5)	43 (5.8)	26 (5.2)

[a]Numbers do not add to 100% because mid-levels of variables, i.e., subclinical depressive and anxious symptoms, somewhat worried, and somewhat lonely, are not shown due to space constraints; UCLA loneliness information was collected only in non-active health care workers.
[b]Participants' own education attainment in GUTS (unmarried category did not apply).

Table 2. Spearman correlations between forms of distress among persons with a positive SARS-CoV-2 test from April 2020 to April 2021, NHS II, NHS3, and GUTS, *N* = 3663

	History of depression	Depressive symptoms	Anxiety symptoms	Worry about COVID	Perceived stress	Loneliness
History of depression	1.0	–	–	–	–	–
Depressive symptoms	$\rho = 0.20^*$	1.0	–	–	–	–
Anxiety symptoms	$\rho = 0.13^*$	$\rho = 0.63^*$	1.0	–	–	–
Worry about COVID	$\rho = 0.05^*$	$\rho = 0.23^*$	$\rho = 0.30^*$	1.0	–	–
Perceived stress	$\rho = 0.10^*$	$\rho = 0.54^*$	$\rho = 0.54^*$	$\rho = 0.23^*$	1.0	–
Loneliness	$\rho = 0.15^*$	$\rho = 0.47^*$	$\rho = 0.32^*$	$\rho = 0.13^*$	$\rho = 0.39^*$	1.0

Note. NHS, Nurses' Health Study; GUTS, Growing Up Today Study. Perceived stress and loneliness were queried in non-active health care workers only.
*$p < 0.001$.

not very worried about COVID-19, those reporting being very worried were more likely to be female, to be racial or ethnic minorities, to be frontline healthcare workers, to have a higher BMI, and to have a comorbidity. Lonely participants were younger than participants who were hardly ever lonely. Chronic depression and all forms of distress at baseline were correlated (Table 2, all $p < 0.001$), with depression and anxiety most strongly correlated (Spearman correlation = 0.63). Despite appearing to be similar constructs, each of the 2 items that comprised the GAD-2 anxiety measure was only modestly correlated with worry about COVID-19 (rho = 0.29, 0.26, $p < 0.001$).

All subsequent analyses were conducted among the 3663 respondents with a positive SARS-CoV-2 test during follow-up. Of these, 132 (4%) were hospitalized due to COVID-19, of whom 75% received oxygen and 20% reported ICU admission. Chronic depression prior to the pandemic was significantly associated with COVID-19 hospitalization (risk ratio (RR) = 1.72; 95% confidence interval (CI) 1.20–2.46, Fig. 1) adjusted for demographic factors. Probable depression at baseline was also associated with COVID-19 hospitalization (RR = 1.81; 95% CI 1.08–3.03, $p = 0.02$, Table 3). In analyses examining depressive symptoms as a continuous measure, an IQR increase in depressive
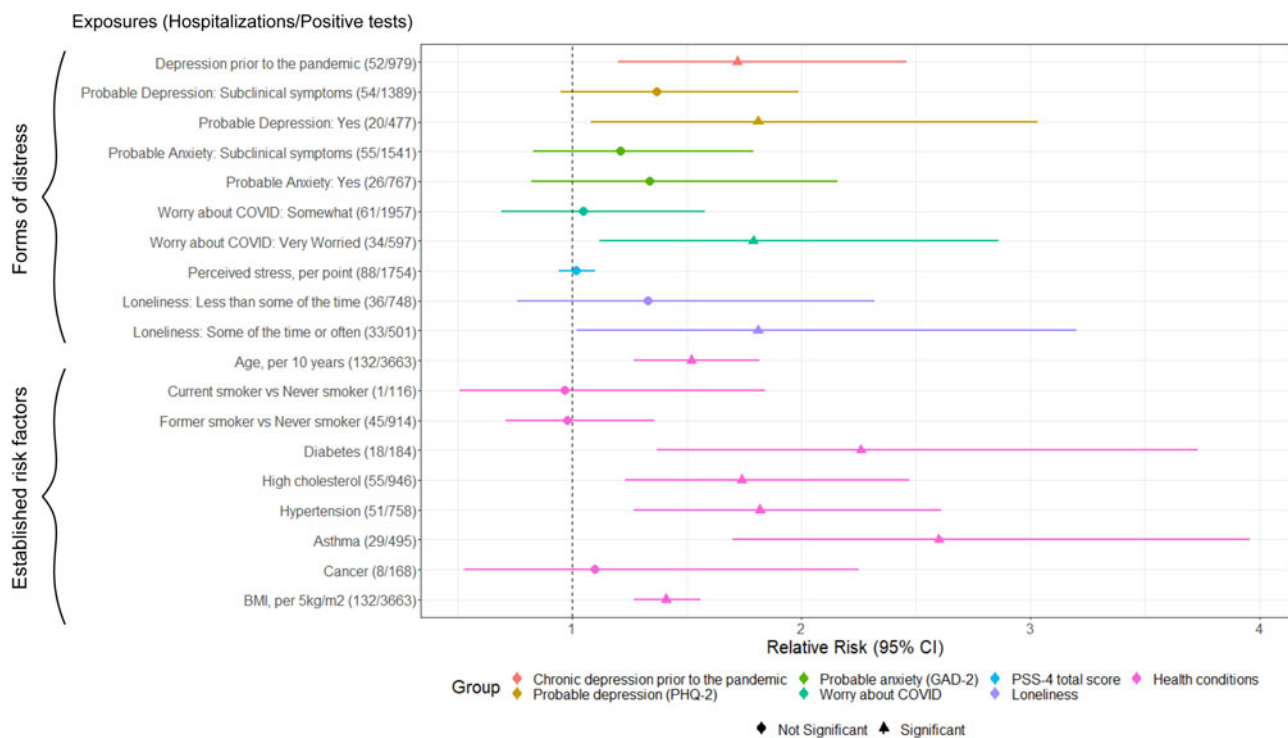

Fig. 1. Relative Risks (RRs) and 95% Confidence Intervals (CIs) of the associations between forms of distress at baseline and established risk factors for severe COVID-19 in relation to COVID-19 hospitalization, April 2020 – April 2021, *N* = 3663. Multivariable model adjusted for age, sex, racial identity, healthcare worker status and partner's education (participants' own education attainment in GUTS). Perceived stress and loneliness were queried in non-active health care workers only.
Note. PHQ-2, 2-item Patient Health Questionnaire; GAD-2, 2-item Generalized Anxiety Disorder.

Table 3. Association of forms of distress prior to infection and risk of COVID-19 hospitalization among persons testing positive for SARS-CoV-2, April 2020 – April 2021, $N = 3663$

	Hospitalized/ Positive tests (N)	Model 1: age, sex, and racial identity, healthcare worker status, and partner's education	Model 2: Model 1 further adjusted for smoking and BMI	Model 3: Model 2 further adjusted for hypertension, diabetes, asthma, high cholesterol, and cancer
		Risk ratio (95% confidence interval)		
Prior to the pandemic				
Chronic depression in the decade prior to the pandemic	52/979	1.72 (1.20–2.46)**	1.47 (1.02–2.11)*	1.34 (0.93–1.93)
At COVID-19 study baseline				
Probable depression (PHQ-2)				
No (0 points)	58/1790	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Subclinical symptoms (1–2 points)	54/1389	1.37 (0.95–1.99)	1.30 (0.90–1.89)	1.26 (0.87–1.83)
Yes (3–6 points)	20/477	1.81 (1.08–3.03)*	1.59 (0.95–2.67)	1.46 (0.87–2.46)
Depressive symptoms, continuous, per approximate IQR		1.45 (1.17–1.81)***	1.37 (1.10–1.71)**	1.32 (1.06–1.65)*
Probable anxiety (GAD-2)				
No (0 points)	51/1349	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Subclinical symptoms (1–2)	55/1541	1.21 (0.83–1.79)	1.20 (0.81–1.76)	1.18 (0.80–1.74)
Yes (3–6 points)	26/767	1.34 (0.82–2.16)	1.23 (0.76–2.00)	1.16 (0.71–1.88)
Anxiety symptoms, continuous, per approximate IQR		1.18 (0.94–1.48)	1.14 (0.91–1.43)	1.11 (0.88–1.39)
Worry about COVID				
Not at all/not very worried	37/1105	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Somewhat worried	61/1957	1.05 (0.69–1.58)	0.98 (0.65–1.47)	0.97 (0.64–1.46)
Very worried	34/597	1.79 (1.12–2.86)*	1.55 (0.96–2.48)	1.51 (0.94–2.42)
p trend[a]		0.02*	0.10	0.12
Among participants who indicated they were not currently frontline healthcare workers ($n = 1754$)				
Perceived stress, per approximate IQR	88/1754	1.09 (0.79–1.49)	1.04 (0.76–1.41)	1.00 (0.73–1.36)
Loneliness				
Hardly ever (3 points)	19/489	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Less than some of the time (4-5 points)	36/748	1.33 (0.76–2.32)	1.26 (0.72–2.20)	1.22 (0.70–2.14)
Some of the time or often (6-9 points)	33/501	1.81 (1.02–3.20)*	1.67 (0.95–2.97)	1.58 (0.89–2.81)
Loneliness score, continuous, per approximate IQR		1.29 (1.01–1.65)*	1.23 (0.96–1.56)	1.20 (0.94–1.53)

Note. PHQ-2, 2-item Patient Health Questionnaire-2; GAD-2, 2-item Generalized Anxiety Disorder; perceived stress and loneliness were queried in non-active health care workers only. IQR, interquartile range.
[a]*p* trend analysis used indicator levels as a continuous variable.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

symptoms was associated with 45% increased risk of COVID-19 hospitalization (95% CI 17–81%, $p < 0.001$).

Worry about COVID-19 was significantly associated with COVID-19 hospitalization (very worried, RR = 1.79; 95% CI 1.12–2.86; p trend = 0.02), as was loneliness (RR = 1.81, 95% CI 1.02–3.20, $p = 0.04$). An IQR increase in the continuous loneliness score was associated with 29% increased risk of COVID-19 hospitalization (95% CI 1–65%, $p = 0.04$). Anxiety and perceived stress were not associated with hospitalization, although perceived stress could only be assessed in non-healthcare workers. Figure 1 shows risk ratios for hospitalization associated with forms of distress

and, for comparison, several established risk factors for severe COVID-19. The magnitude of the associations with COVID-19 hospitalization was as strong for chronic depression prior to the pandemic and worry about COVID-19 at baseline as for hypertension and high cholesterol.

In models further adjusted for smoking and BMI (Table 3, model 2), associations between chronic depression, depression at baseline, worry, and loneliness and COVID-19 hospitalization were attenuated (attenuation range, 13–29%). Higher BMI among persons with distress accounted for most of the attenuation. Associations were further attenuated after adjustment for

comorbidities (additional attenuation, 6–25%; total attenuation due to all covariates, 23–46%), primarily due to the higher prevalence of asthma among persons with distress. Depressive symptoms coded continuously remained significantly associated with increased risk for COVID-19 hospitalization in the model fully adjusted for health behaviors and comorbidities (RR per IQR = 1.32, 95% CI 1.06–1.65, $p = 0.01$).

Associations of distress with COVID-19 hospitalization were generally somewhat stronger in non-healthcare workers than healthcare workers, though these differences were not statistically significant (data not shown). Results were comparable in models further adjusted for month, excluding probable baseline SARS-CoV-2 cases, excluding cases diagnosed within 30 days after return of baseline questionnaire, further adjusting for cohort number, restricting the analysis to female, and using the most recent distress measures prior to infection. In analyses of loneliness, results were similar in models further adjusted for living alone (online Supplementary Table S4).

Discussion

In this prospective study of 54 809 people who reported no history of SARS-CoV-2 infection, in demographically adjusted models, chronic depression prior to the pandemic, and probable depression, worry about COVID-19, and loneliness early in the pandemic were associated with increased risk for hospitalization due to COVID-19, among the 3663 individuals who subsequently became infected with SARS-CoV-2. There was no association of anxiety or perceived stress with risk of hospitalization, although we were not able to assess perceived stress among healthcare workers. Depression, worry about COVID-19, and loneliness were as strongly associated with hospitalization as were established risk factors for COVID-19 severity, such as high cholesterol and hypertension.

Higher prevalence of risk factors for COVID-19 severity, in particular, higher BMI and asthma accounted for 23–46% of these associations. In fully adjusted models accounting for all comorbidities, only depressive symptoms at baseline remained significantly associated with risk of COVID-19 hospitalization. We did not have information about whether distress preceded weight gain and asthma or the reverse. Evidence from longitudinal studies suggests a bi-directional association of depression and high BMI, with depression increasing risk of subsequent obesity and obesity increasing the risk of subsequent depression. Longitudinal and Mendelian randomization studies also indicate bi-directional effects between depression and adult-onset asthma, although evidence that asthma predicts incident depression is not consistent (Gao et al., 2015; Kim, Min, Oh, Lim, & Choi, 2019; Lehto, Pedersen, Almqvist, Lu, & Brew, 2019; Lu et al., 2018; Zhu et al., 2019). Mendelian randomization studies show causal effects of both BMI and body fat on loneliness, but not loneliness on BMI (Abdellaoui et al., 2019; Day, Ong, & Perry, 2018); however, the direction of causality with asthma has not been well studied. Therefore, depression and loneliness may have increased risk of obesity and asthma, and obesity and asthma may also have increased risk of depression and loneliness.

A single prior study using data from the UK Biobank assessed depressive and anxious symptoms with the PHQ-4 in 2006–2010 and found an association between these symptoms and susceptibility to SARS-CoV-2 infection and COVID-19 hospitalization over an 1-year period in age- and sex-adjusted models, but not after further adjustment for ethnicity, comorbidity, and lifestyle factors (Batty et al., 2020). However, the study conflated risk of infection and risk of hospitalization, as the reference group included people uninfected with SARS-CoV-2 and people infected with SARS-CoV-2 who were not hospitalized. As risk factors for SARS-CoV-2 infection and COVID-19 severity may differ (Yang, Gui, & Xiong, 2020b), the implications of these findings are unclear.

Chronic depression is pro-inflammatory and immunosuppressive (Leonard, 2010). Psychological distress, more generally, may increase risk of severe clinical outcomes in respiratory infections (Aiello, Simanek, Stebbins, & Dowd, 2018; Bu et al., 2020; Falagas et al., 2010; LeRoy et al., 2017), possibly through dysregulation of stress signaling pathways. Sustained stress leads to protracted HPA-axis stimulation and subsequent chronic immune suppression (Guilliams & Edwards, 2010) as well as elevated levels of circulating cortisol (Hannibal & Bishop, 2014), which leads to susceptibility to infection and more severe clinical outcomes among those infected (Tian, Hou, Li, & Yuan, 2014). Chronic exposure to elevated cortisol may additionally result in an inability to attenuate levels of pro-inflammatory cytokines post-infection (Chi et al., 2013; Cohen et al., 1997; Tian et al., 2014), which further compounds disease severity (Del Valle et al., 2020; Short, Kroeze, Fouchier, & Kuiken, 2014; Zhao et al., 2018) and increases risk of hospitalization (Yende et al., 2005). Despite common pathways linking depression, anxiety, stress, and loneliness to immune dysregulation, we did not find associations of anxiety and perceived stress with hospitalization risk. Of note, perceived stress has not been consistently associated with physical health outcomes (Macleod et al., 2002; Väänänen et al., 2009).

The present study was conducted in a primarily female sample. Prior studies have suggested men with COVID-19 may face higher rates of hospitalization than women. A systematic review of COVID-19 outcomes in Europe found that men with COVID-19 experienced higher rates of hospitalization than women (Gebhard, Regitz-Zagrosek, Neuhauser, Morgan, & Klein, 2020). Multicenter cohort studies have similarly found higher rates of COVID-19 hospitalization in men vs. women, although these studies were not adjusted for factors which may affect hospitalization, such as age and health comorbidities (Garg et al., 2020; Gomez et al., 2021). Past studies of SARS-CoV and MERS-CoV outbreaks have also found men to have higher case fatality rates than women (Ebrahim et al., 2021; Karlberg, Chong, & Lai, 2004). Additional research is therefore needed to investigate the association of distress with risk of COVID-19 hospitalization in men.

Our study has several strengths. Periodic surveys were sent to three large cohorts prospectively measuring distress, incident infection, and hospitalization over a 1-year period during an active stage of the COVID-19 pandemic. Distress was measured early in the pandemic, which may have more accurately captured recent distress compared with studies examining pre-pandemic medical records of mental illness. Findings were also robust to exclusion of persons with COVID-19 diagnosis within 30 days of the baseline questionnaire. We examined some largely unexplored forms of distress, such as loneliness, perceived stress, and worry about COVID-19.

Our study has several limitations. Baseline anxiety and depression were measured with brief screeners rather than clinician diagnoses and may have been misclassified. Worry about COVID-19 was measured with a single question, which may have lower reliability than a multi-item measure

(Diamantopoulos, Sarstedt, Fuchs, Wilczynski, & Kaiser, 2012). SARS-CoV-2 infection and hospitalization due to COVID-19 were self-reported, although self-reported health outcomes have had good validity in these cohorts (Forman, Curhan, & Taylor, 2008; Troy et al., 1995). We were not able to capture COVID-19-related mortality. Finally, our sample of individuals infected with COVID-19 was relatively small, limiting statistical power, and was comprised primarily of white female nurses, limiting generalizability.

Conclusions

In this prospective study of adults, we found chronic depression prior to the pandemic and probable depression, worry about COVID-19, and loneliness predicted hospitalization due to COVID-19, which was in part accounted for by poorer physical health in persons with these forms of distress. Depressive symptoms early in the pandemic remained associated with COVID-19 hospitalization even after adjusting for health-related behaviors and comorbidities. Our findings suggest the need to consider psychological health in addition to physical health as risk factors of severe COVID-19. Future research should examine whether reducing distress, in addition to other medical interventions, improves outcomes in patients with SARS-CoV-2 and other infectious diseases.

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