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Association of depressive symptoms with incidence and mortality rates of COVID-19 over 2 years among healthcare workers in 20 countries: multi-country serial cross-sectional study

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Abstract

Background Long-term deterioration in the mental health of healthcare workers (HCWs) has been reported during and after the COVID-19 pandemic. Determining the impact of COVID-19 incidence and mortality rates on the mental health of HCWs is essential to prepare for potential new pandemics. This study aimed to investigate the association of COVID-19 incidence and mortality rates with depressive symptoms over 2 years among HCWs in 20 countries during and after the COVID-19 pandemic.

Methods This was a multi-country serial cross-sectional study using data from the first and second survey waves of the COVID-19 HEalth caRe wOrkErS (HEROES) global study. The HEROES study prospectively collected data from HCWs at various health facilities. The target population included HCWs with both clinical and non-clinical roles. In most countries, healthcare centers were recruited based on convenience sampling.

As an independent variable, daily COVID-19 incidence and mortality rates were calculated using confirmed cases and deaths reported by Johns Hopkins University. These rates represent the average for the 7 days preceding the participants' response date. The primary outcome was depressive symptoms, assessed by the Patient Health Questionnaire-9. A multilevel linear mixed model (LMM) was conducted to investigate the association of depressive symptoms with the average incidence and mortality rates.

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Results A total of 32,223 responses from the participants who responded to all measures used in this study on either the first or second survey, and on both the first and second surveys in 20 countries were included in the analysis. The mean age was 40.1 (SD = 11.1), and 23,619 responses (73.3%) were from females. The 9323 responses (28.9%) were nurses and 9119 (28.3%) were physicians. LMM showed that the incidence rate was significantly and positively associated with depressive symptoms (coefficient = 0.008, standard error 0.003, $p = 0.003$). The mortality rate was significantly and positively associated with depressive symptoms (coefficient = 0.049, se = 0.020, $p = 0.017$).

Conclusions This is the first study to show an association between COVID-19 incidence and mortality rates with depressive symptoms among HCWs during the first 2 years of the outbreak in multiple countries. This study's findings indicate that additional mental health support for HCWs was needed when the COVID-19 incidence and mortality rates increase during and after the early phase of the pandemic, and these findings may apply to future pandemics.

Trial registration Clinicaltrials.gov, NCT04352634.

Keywords COVID-19, Incidence rate, Mortality rate, Depressive symptoms, Healthcare worker, Multi-country study, Serial cross-sectional study

Manuscript

Background

Deterioration in the mental health of healthcare workers (HCWs) has been reported not only in the early stages of the novel coronavirus disease (COVID-19) pandemic [1–7], but also in the long term during and after the COVID-19 pandemic [8–25]. Mental health problems have been associated with absenteeism, job performance, and intention to leave [26–28]. Prevention and countermeasures for mental health problems among HCWs are essential for sustaining the healthcare system. Few studies have examined long-term mental health outcomes among HCWs during and after the COVID-19 pandemic, and the long-term factors related to mental health among HCWs have not been adequately elucidated [13, 29–33]. Therefore, it is necessary to investigate the factors associated with the long-term mental health deterioration among HCWs during and after the COVID-19 pandemic.

The severity of the COVID-19 outbreak, measured by the incidence and mortality rates of COVID-19, has been reported in many cross-sectional studies as a salient factor associated with increased mental health issues [30, 34–38]. The incidence and mortality rates are factors that increase and decrease over time, which warrant data-recording and analytical approaches adequate to model such time-varying nature. In the context of high COVID-19 incidence rates, HCWs may have experienced deterioration in their mental health due to increased workload, changes in work activities, increased risk of infection, worsening of their fear of infection, and limited access to adequate PPE, among other reasons [39]. Similarly, an increase in the COVID-19 related mortality rate may have led to a deterioration in the mental health of HCWs due to traumatic experiences such as the death of a patient or fear of their own death [40, 41]. Determining the impact of COVID-19 incidence and mortality rates on the mental health of HCWs is essential to prepare for future pandemics.

There are some essential gaps in prior studies of COVID-19 incidence and mortality rates and long-term mental health outcomes [42–45]. First, no study has investigated the long-term and time-related association between the country's mortality rate and HCWs' mental health during and after the COVID-19 pandemic. Second, long-term associations between the incidence rate and mental health have been reported in single-region or country-specific studies but not in a multi-country study. It is unclear whether the long-term association between the incidence or mortality rate and mental health varies by country or between high-income and low-and-middle-income countries. Third, to our knowledge, there was only one study with depressive symptoms as an outcome, which examined the long-term associations between the incidence rate and depressive symptoms. In the previous study in New York City, daily changes in the local and national incidence rate were modestly correlated with changes in daily mean depressive symptoms among HCWs from May 2020 to January 2021 [44]. Fourth, the timeframe of previous studies was only one year at the most during the COVID-19 pandemic. It is not clear whether the incidence and mortality rates were associated with depressive symptoms among HCWs only during the early phase of the COVID-19 pandemic or also long-term during the COVID-19 pandemic. Therefore, further research using long-term and multi-country data is needed to elucidate the direction and strength of the association of COVID-19 incidence and mortality rates with depressive symptoms. This research may reveal changes in depressive symptoms over time and identify when mental health support for HCWs is needed. Therefore, if these research gaps are studied and show long-term associations over two years between incidence rate and mortality rate and depressive symptoms, long-term factors associated with depressive symptoms can be clarified, and prevention and improvement of long-term depressive symptoms from the early stages of an outbreak can be expected. The results of this study may not only help identify when depressive symptoms become severe and the need to take countermeasures, but also help prevent deterioration by identifying when depressive symptoms gradually worsen from their usual state and take preventive measures.

Accordingly, the present study aimed to investigate the association of depressive symptoms with the prior week's incidence and mortality rates of COVID-19 over 2 years among HCWs in 20 countries during and after the COVID-19 outbreak. In addition, this study aimed to investigate whether the association of depressive symptoms with the incidence and mortality rates of COVID-19 varied by factors such as individual characteristics and whether the participants lived in a high-income or low-and-middle-income country.

Methods

Study design

The design of this study was a multi-country serial cross-sectional study using multiple waves of survey data. Data were retrieved from the first and second surveys of the international COVID-19 HEalth caRe wOrkErS (HEROES) study. The HEROES study aimed to assess the impact of the COVID-19 pandemic on HCWs' mental health [38, 46, 47]. While the HEROES study used a prospective cohort design that included HCWs from pre-selected healthcare facilities in the participating countries, the present analysis captures the data from the first and second surveys, which occurred during a 2-year timeframe, thus allowing to examine the effect of time-varying stressors linked to the evolving, dynamic nature of the pandemic. The reason for using data from the first and second surveys was to examine the long-term association between the incidence and mortality rates were associated with depressive symptoms from the early stages of the COVID-19 pandemic, as well as because fewer countries conducted surveys after the second survey. The target population included HCWs with both clinical and non-clinical roles (e.g., physicians, nurses, psychologists, dentists, managers, administrative staff, security, cleaning staff) employed in a wide range of healthcare centers (e.g., hospitals, primary care centers, mental health facilities, elderly homes, rehabilitation centers, emergency medical services) in the 24 participating countries. Healthcare centers were recruited in most countries based on convenience sampling; however, facilities were randomly selected in Brazil, Colombia, Japan, and Lebanon. Sites recruited participants by sharing a link to the study's digital platform via their work email address or the healthcare center's internal communication system. The recruitment period for the first survey of the HEROES study varied by country, with the first survey taking place after March 2020 and the second survey taking place 6 months after the first survey in the countries where the second survey was conducted. In most countries, recruitment of the first survey took place during the first wave of the pandemic, at a time when vaccines were scarcely available. The reason why the timing of the first survey differed from country to country was that the survey was started in countries that were ready to begin the survey in order to obtain data from the early stages of the COVID-19 pandemic, which was unpredictable and sudden. The second survey was intended to take place 6 months after the first survey, but in some cases the survey took place after 6 months. Participants generally participated in the longitudinal survey, although some participants began participating in the second survey. An online questionnaire based on standardized measures and ad hoc items was employed. The study used a secure platform based on the REDCap model [48, 49], which was designed to ensure data security and quality. This system was created ad hoc to facilitate translation into different languages, making the survey available in all participants' languages.

This study was approved by accredited Institutional Review Boards (IRBs) in each participating country. This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [50, 51].

Participants

The target population included HCWs with both clinical and non-clinical roles employed in a wide range of healthcare centers in the participating countries. The inclusion criteria for potential participants included being of legal age, working in one of the preselected health facilities, working in a health facility that provides care to confirmed or suspected cases of COVID-19, and having an internet connection to answer the online questionnaire.

Measurements

Outcome

Depressive symptoms were measured by the Patient Health Questionnaire-9 (PHQ-9) and used as a continuous score in this study. The PHQ-9 is a self-report questionnaire developed to assess depressive symptoms by rating one's condition for the previous 2 weeks [52]. PHQ-9 was answered by participants at the first and second surveys. The validity and reliability of the various language versions have been verified [52, 53]. The PHQ-9 is recommended as an international measure of depressive symptoms by the Common Measures in Mental Health Science Initiative [54, 55].

Independent variables

The incidence and mortality rates of COVID-19 were calculated as a moving average of the 7 days prior to each participant's response date based on the number of daily confirmed COVID-19 cases and deaths in each country as reported by the COVID-19 Data Repository at Johns Hopkins University [56]. The incidence rate was calculated as the number of COVID-19 cases per 100,000 population, and the mortality rate was calculated by dividing the number of recorded deaths by the number of COVID-19 cases and then multiplying by 100 to obtain a percentage [56].

In addition, four researchers (HA, KW, YM, and DN) discussed the time period for calculating the incidence and mortality rates of COVID-19 with reference to the previous studies [38, 44]. There was a possibility of errors in government statistics for any particular day of the week, and the participant might not know the incidence and mortality rates of COVID-19 of their response date. As a result of the discussion, it was decided that the average incidence and mortality rates of COVID-19 from 7 days to 1 day prior to the response date would be more appropriate than the incidence and mortality rates on the response date. Thus, the incidence and mortality rates of COVID-19 in this study were defined as the average incidence and mortality rates of COVID-19 over the 7 days preceding the date the participants responded (Additional file 1: Figure S1 and Figure S2).

Demographic variables

Questions about age, gender, occupation, experience of contact with patients who had suspected or confirmed cases of COVID-19, and history of mental health problems were initially developed in the HEROES study [47]. The occupation was categorized into five groups based on a previous study: physicians, nurses, other HCWs (e.g., psychologist, social worker, radiology technician, laboratory technician, physical therapist, respiratory therapist, dietician, dentist, occupational therapist, speech therapist, first responder, clinical manager/director, social-community mental health worker), ancillary workers (e.g., non-clinical manager, administrator/secretary/admission, patient transportation, food/hospitality, cleaning staff, maintenance staff, security staff), and other [38]. The question about the experience of contact with patients who were suspected or confirmed cases of COVID-19 was "During the past week, have you been close to patients who were suspected or confirmed cases of COVID-19?" and answered with three choices (yes/ no/ I don't know). The question about the history of mental health problems was "Before the pandemic, did you have a mental health diagnosis?" and answered with three choices (yes/ no/ I don't know). Based on the DAC List of ODA Recipients for reporting on aid in 2022 and 2023 published by the Organization for Economic Co-operation and Development, participants' countries of residence were classified as high-income countries (Chile, Czech Republic, Germany, Italy, Japan, Netherlands, Saudi Arabia, Spain, and Uruguay) or low-and-middle-income countries (Argentina, Armenia, Bolivia, Brazil, Colombia, Guatemala, Mexico, Nigeria, Peru, Tunisia, and Venezuela) [57].

Statistical analysis

We analyzed the dataset of responses of the participants who responded to all measures used in this study on either the first or second survey, and on both the first and second surveys. Missing values were considered missing not at random because some variables were not measured in some countries, so all participants in those countries had missing values for those variables, and participants with severe depressive symptoms may have had missing values because they had difficulty responding to the PHQ-9. We did not adopt any imputation methods because missing in the present study should occur not at random and imputations were problematic. Most of the excluded participants in this study responded only once and did not respond to all of the measures used. The participants with missing values might have had systematic differences from the completers. Instead, we compared and reported statistical differences in demographic characteristics. Mann–Whitney U tests for continuous variables, and Pearson's chi-squared tests for categorical variables were used to compare variables between the analyzed and excluded responses. The average incidence and mortality rates of COVID-19 and PHQ-9 were calculated for the entire period of this study, each year, and each month based on the participants' response dates, regardless of the first and second surveys. The intraclass correlation coefficients (ICC) within countries for PHQ-9 were calculated for all responses of the analyzed participants.

Multilevel linear mixed models (LMM) were conducted to investigate the association of depressive symptoms with the incidence and mortality rates [58, 59]. The data were conceptualized as a two-level model, consisting of individuals at the first level and countries at the second level. We used restricted maximum likelihood (ReML) estimation for all LMM analyses [60]. Three steps of multilevel LMM were conducted. The first step of the analysis was performed without explanatory variables (null model: Model 1). This model contains a random effect between countries of the intercept for the depressive symptoms and the fixed effect of time. The time effect was coded as a daily-level continuous variable based on the survey period, with January 1, 2020, as 0. The outcome, the PHQ-9, was used at the daily-level based on the participant's response date. The incidence or mortality rates were entered into Model 2 (crude model). The average incidence and mortality rates of COVID-19 from 7 days to 1 day prior to the response date were also used at the daily-level based on the participant's response date. The demographic and work-related variables were entered into Model 3 (adjusted model) as the covariates. Akaike information criteria (AIC) was calculated to check the model fit [61–63]. In model 3 of the multilevel linear mixed model (LMM), the grand mean centered on age established a useful zero point, and dummy variables were created for gender, occupation, contact with patients who had suspected or confirmed cases of COVID-19, and history of mental health problems. The equation for Model 3 could be explained as follows;

Level 1 (individual level)

$$\begin{aligned} Y(depressive\ symptoms: PHQ-9)_{ijt} &= \beta_{0j} + \beta_1 * (age)_{ijt} + \beta_2 * (gender: female)_{ijt} + \beta 3 * (gender: other\ gender)_{ijt} \\ &+ \beta_4 * (Occupation: nurses)_{ijt} + \beta_5 * (Occupation: other\ healthcare\ workers)_{ijt} \\ &+ \beta_6 * (Occupation: ancillary\ workers)_{ijt} + \beta_7 * (Occupation: other)_{ijt} \\ &+ \beta_8 * (Contact\ with\ patients\ who\ had\ suspected\ or\ confirmed\ cases\ of\ COVID-19: yes)_{ijt} \\ &+ \beta_9 * (Contact\ with\ patients\ who\ had\ suspected\ or\ confirmed\ cases\ of\ COVID-19: I\ do\ not\ know)_{ijt} \\ &+ \beta_{10} * (History\ of\ mental\ health\ problems: yes)_{ijt} + \beta_{11} * (History\ of\ mental\ health\ problems: I\ do\ not\ know)_{ijt} + e_{ijt} \end{aligned}$$

Level 2 (country level)

$$\beta_{0jt} = \gamma 00 * (incidence\ rate\ or\ mortality\ rate\ of\ COVID-19)_{jt} + \varepsilon_{0jt}$$

$$\varepsilon_{0jt} \sim \left(0, \sigma^2\right)$$

Note: Y_{ijt} means the score of depressive symptoms of individual healthcare worker j who lived in a country i at Time t. ε_{0jt} means a random effect, and e_{ijt} means a residual.

Three similar steps of multilevel LMMs were conducted in each of the subgroups classified by gender (men and women), occupation (physicians, nurses, other HCWs, ancillary workers, and others), contact with patients who had suspected or confirmed cases of COVID-19 (yes, and no), history of mental health problems (yes, and no), and high-income and low-and-middle-income countries. As a sensitivity analysis, similar multilevel LMMs were conducted on 30,520 responses, including the 28,817 responses which were responded to either the first or second survey, and only the responses to the first survey from the 1703 participants who responded to both the first and second surveys.

The statistical significance level was set at a p value of less than 0.05. All analyses were conducted by using SPSS version 29.0 J for Windows (SPSS, Tokyo, Japan).

Results

Participants flow

The 37,105 participants from 24 countries (Argentina, Armenia, Belgium, Bolivia, Brazil, Chile, Colombia, Czech Republic, Germany, Guatemala, Italy, Japan, Lebanon, Mexico, Netherlands, Nigeria, Peru, Puerto Rico, Saudi Arabia, South Africa, Spain, Uruguay, Tunisia, and Venezuela) participated in the first survey. The 15,117 participants from 14 countries (Argentina, Armenia, Chile, Colombia, Czech Republic, Guatemala, Japan, Mexico, Netherlands, Nigeria, Peru, Puerto Rico, and Spain, Tunisia) participated in the second survey. From the first and second surveys, 52,222 responses were collected from 24 countries (Argentina, Armenia, Belgium, Bolivia, Brazil, Chile, Colombia, Czech Republic, Germany, Guatemala, Italy, Japan, Lebanon, Mexico, Netherlands, Nigeria, Peru, Puerto Rico, Saudi Arabia, Tunisia, Venezuela, South Africa, Spain, and Uruguay). The 19,999 responses that did not respond to the variables used in this study were excluded. All participants in 4 countries (Belgium, Lebanon, Puerto Rico, and South Africa) were excluded because they did not respond to the variables used in this study, such as PHQ-9. Thus, 32,223 responses from 30,520 participants in 20 countries (Argentina, Armenia, Bolivia, Brazil, Chile, Colombia, Czech Republic, Germany, Guatemala, Italy, Japan, Mexico, Netherlands, Nigeria, Peru, Saudi Arabia, Spain, Tunisia, Uruguay, Venezuela) were included in the analysis. The 28,817 responses were responded to either the first or second survey, and the 1703 participants who responded to both the first and second surveys (Fig. 1).

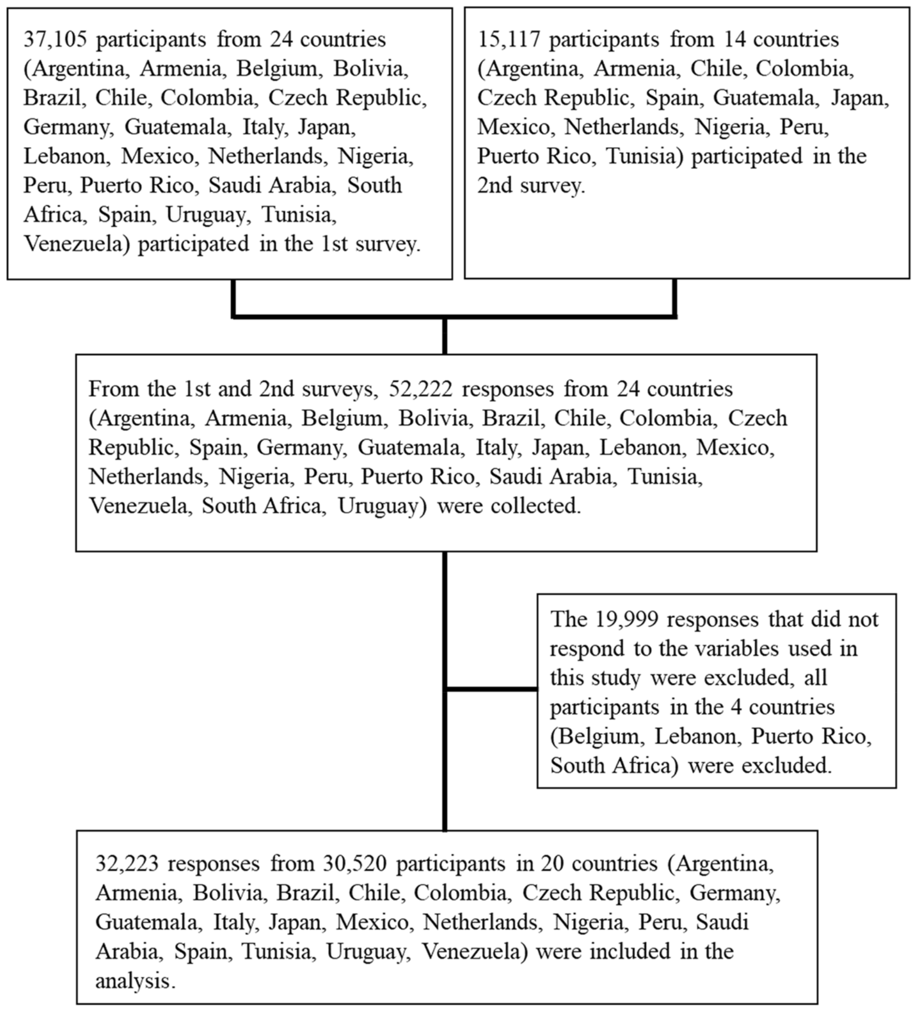

Fig. 1 Participant flow. The design of this study was a multi-country serial cross-sectional study, not a longitudinal study, although data were retrieved from the first and second surveys of the international COVID-19 HEalth caRe wOrkErS (HEROES) study. We analyzed the dataset of responses of the participants who responded to all measures used in this study

Participant characteristics

The mean age was 40.1 years (SD = 11.1); 23,619 responses (73.3%) were from women, 9323 (28.9%) were nurses, and 9119 (28.3%) were physicians (Table 1). The mean PHQ-9 score was 6.0 (SD = 5.5). The ICC within countries for the PHQ-9 was 0.07 among all analyzed participants' responses.

The mean incidence rate of COVID-19 for the entire period of this study was 11.90 (SD = 16.46), 6.77 (SD = 7.78) in 2020, 20.87 (SD = 22.73) in 2021, and 12.00 (SD = 8.80) in 2022 (Table 2). The mean mortality rate of COVID-19 for the entire period of this study was 6.47 (SD = 4.96), 7.70 (SD = 5.32) in 2020, 4.42 (SD = 3.37) in 2021, and 2.28 (SD = 0.01) in 2022. The number of responses from the analyzed participants each month for each country is shown in Table S1 (Additional file 1: Table S1). The earliest response date was April 24, 2020, and the latest was March 5, 2022, and there were participant responses every month during this period.

The results of Mann–Whitney U tests and Pearson's chi-square tests, gender ($p < 0.01$), age (the analyzed responses 40.1 years, the excluded responses 38.6 years; $p < 0.01$), occupation ($p < 0.01$), the experience of contact with patients who had suspected or confirmed cases of COVID-19 ($p < 0.01$), history of mental health problems ($p < 0.01$), country ($p < 0.01$), the incidence rate of COVID-19 (the analyzed responses 11.9, the excluded responses 22.6; $p < 0.01$) and the mortality rate of COVID-19 (the analyzed responses 6.5, the excluded responses 5.7; $p < 0.01$) were significantly different between the analyzed responses ($n = 32{,}223$) and the excluded responses ($n = 19{,}999$) (Table 3). There was no significant difference in PHQ-9 scores between the analyzed and excluded responses.

Table 1 Characteristics of the participants ($N = 32{,}223$)

Variables	N	%	Mean	SD
Gender				
Male	8563	26.6%		
Female	23,619	73.3%		
Other gender	41	0.1%		
Age (years)			40.1	11.1
Occupation				
Physicians	9119	28.3%		
Nurses	9323	28.9%		
Other healthcare workers[a]	6989	21.7%		
Ancillary workers[b]	3976	12.4%		
Other	2816	8.7%		
Contact with patients who had suspected or confirmed cases of COVID-19				
No	10,516	32.6%		
Yes	16,065	49.9%		
I do not know	5642	17.5%		
History of mental health problems and drugs				
No	27,369	84.9%		
Yes	4561	14.2%		
I do not know	293	0.9%		
Country				
Argentina	1483	4.6%		
Armenia	292	0.9%		
Bolivia	109	0.3%		
Brazil	2377	7.4%		
Chile	2982	9.3%		
Colombia	2437	7.6%		
Czech Republic	1344	4.2%		
Germany	159	0.5%		
Guatemala	1265	3.9%		
Italy	4189	13.0%		
Japan	1078	3.3%		
Mexico	6476	20.1%		
Netherlands	407	1.3%		
Nigeria	273	0.8%		
Peru	1351	4.2%		
Saudi Arabian	118	0.4%		
Spain	3204	9.9%		
Tunisia	458	1.4%		
Uruguay	1629	5.1%		
Venezuela	592	1.8%		
PHQ-9 (range 0–27)			6.0	5.5

SD standard deviation, *COVID-19* novel coronavirus disease 2019, *PHQ-9* Patient Health Questionnaire-9

[a] Other healthcare workers: e.g., psychologist, social worker, radiology technician, laboratory technician, physical therapist, respiratory therapist, dietician, dentist, occupational therapist, speech therapist, first responder (Paramedic/EMT), clinical manager/director, social-community mental health worker

[b] Ancillary workers: e.g., non-clinical manager, administrator/secretary/admission, patient transportation, food/hospitality, cleaning staff, maintenance staff, security staff

Association between incidence or mortality rate of COVID-19 and depressive symptoms

Multilevel LMM showed that time was significantly negatively associated with depressive symptoms in model 1 (coefficient = −0.003, se = 0.000, $p < 0.001$). The incidence rate was significantly positively associated with depressive symptoms in model 2 (coefficient = 0.011, se = 0.003, $p < 0.001$) and model 3 (coefficient = 0.008, se = 0.003, $p = 0.003$) (Table 4). In this multilevel LMM, model 3 had the best model fit (AIC = 194,434.531).

The mortality rate was significantly positively associated with depressive symptoms in model 2 (coefficient = 0.076, se = 0.022, $p < 0.001$) and model 3 (coefficient = 0.049, se = 0.020, $p = 0.017$) (Table 5). In this multilevel LMM, model 3 had the best model fit (AIC = 194,433.259).

In subgroup analyses by gender, there was a significant positive association between the incidence rate of COVID-19 and depressive symptoms in models 2 and 3 in both men and women (Additional file 1: Table S2 and Table S3). There was a significant association in women between the mortality rate of COVID-19 and depressive symptoms in model 2 (coefficient = 0.074, se = 0.026, $p = 0.004$) and model 3 (coefficient = 0.050, se = 0.024, $p = 0.035$), but no significant association in men (Additional file 1: Table S4 and Table S5).

In subgroup analyses by occupation, there was a significant association between the incidence rate of COVID-19 and depressive symptoms in model 2 (coefficient = 0.013, se = 0.005, $p = 0.018$) among physicians, model 2 (coefficient = 0.017, se = 0.005, $p = 0.002$) and model 3 (coefficient = 0.014, se = 0.005, $p = 0.006$) among nurses, and model 2 (coefficient = 0.014, se = 0.006, $p = 0.037$) among other HCWs, but not among ancillary workers and other occupations (Additional file 1: Table S6 to Table S10). There was no significant association between the mortality rate of COVID-19 and depressive symptoms among any of the occupations (Additional file 1: Table S11 to Table S15).

In subgroup analyses by the experience of contact with patients who had suspected or confirmed cases of COVID-19, there was a significant association between the incidence rate of COVID-19 and depressive symptoms in model 2 (coefficient = 0.011, se = 0.005, $p = 0.032$) among participants without the experience of contact with patients who had suspected or confirmed cases of COVID-19, model 2 (coefficient = 0.009, se = 0.004, $p = 0.015$) and model 3 (coefficient = 0.009, se = 0.004, $p = 0.010$) among participants with the experience of contact with patients who had suspected or confirmed cases of COVID-19 (Additional file 1: Table S16 and Table S17). There was

Table 2 The annual and monthly means of the incidence and mortality rates of COVID-19, and PHQ-9

Date	*n*	Incidence rate[a]		Mortality rate[a]		PHQ-9	
		Mean	SD	Mean	SD	Mean	SD
All	32,223	11.90	16.46	6.47	4.96	5.97	5.47
April-December, 2020	20,,328	6.77	7.78	7.70	5.32	6.20	5.45
April, 2020	352	7.13	1.36	10.58	0.22	7.76	5.38
May, 2020	2140	2.07	2.82	12.39	2.20	6.93	5.40
June, 2020	5606	4.51	9.66	11.67	4.50	6.55	5.11
July, 2020	4271	5.82	5.00	6.10	4.70	5.67	5.43
August, 2020	2360	11.44	8.38	6.57	5.42	5.78	5.38
September, 2020	2674	10.49	6.74	4.49	3.20	5.92	5.66
October, 2020	1608	8.86	5.44	2.46	0.87	6.45	5.80
November, 2020	1189	7.48	6.56	2.52	0.87	5.69	5.95
December, 2020	128	18.88	3.26	2.62	0.34	7.27	6.04
January-December, 2021	11,623	20.87	22.73	4.42	3.37	5.58	5.46
January, 2021	8	70.70	20.11	2.23	0.13	13.50	9.90
February, 2021	1815	30.65	21.58	3.67	2.75	5.94	5.13
March, 2021	3338	17.38	14.20	4.09	3.50	5.06	5.28
April, 2021	3817	21.65	30.20	6.53	3.50	5.28	5.40
May, 2021	750	27.19	16.11	2.18	0.75	6.55	5.50
June, 2021	499	19.61	22.94	1.96	0.52	5.62	5.29
July, 2021	227	28.90	8.52	2.46	0.13	6.65	6.06
August, 2021	625	11.88	6.37	2.49	0.13	7.17	6.23
September, 2021	239	3.00	0.12	2.55	0.00	5.59	5.46
October, 2021	294	2.82	0.08	2.55	0.00	6.30	6.61
November, 2021	3	4.62	0.00	2.54	0.00	5.67	4.73
December, 2021	8	3.74	0.00	2.53	0.00	5.50	5.98
January-March, 2022	272	12.00	8.80	2.28	0.01	5.24	5.51
January, 2022	4	51.66	0.00	2.31	0.00	4.25	3.50
February, 2022	181	15.44	5.53	2.28	0.00	4.55	5.52
March, 2022	87	3.01	0.00	2.29	0.00	6.70	5.31

SD standard deviation, *COVID-19* novel coronavirus disease 2019, *PHQ-9* Patient Health Questionnaire-9

[a] Mean of the incidence and mortality rates from 7 days before to the day before the survey day in the participants' country

a significant association between the mortality rate of COVID-19 and depressive symptoms in model 2 (coefficient = 0.087, se = 0.031, $p = 0.005$) among participants with the experience of contact with patients who had suspected or confirmed cases of COVID-19, but no significant association among participants without the experience of contact with patients who had suspected or confirmed cases of COVID-19 (Additional file 1: Table S18 and Table S19).

In subgroup analyses by the history of mental health problems, there was a significant association between the incidence rate of COVID-19 and depressive symptoms in model 2 (coefficient = 0.012, se = 0.003, $p < 0.001$) and model 3 (coefficient = 0.010, se = 0.003, $p < 0.001$) among participants without a history of mental health problems, but no significant association among participants with a history of mental health problems (Additional file 1: Table S20 and Table S21). There was a significant association between the mortality rate of COVID-19 and depressive symptoms in model 2 (coefficient = 0.119, se = 0.052, $p = 0.024$) among participants with a history of mental health problems, but no significant association among participants without a history of mental health problems (Additional file 1: Table S22 and Table S23).

In subgroup analyses in high-income or low-and-middle-income countries, there was a significant association between the incidence rate of COVID-19 and depressive symptoms in model 2 (coefficient = 0.015, se = 0.006, $p = 0.014$) in low-and-middle-income countries, but no significant association in high-income countries (Additional file 1: Table S24 and Table S25). There was a significant positive association between the mortality rate of COVID-19 and depressive symptoms in model 2 and model 3 in both high-income and low-and-middle-income countries (Additional file 1: Table S26 and Table S27).

Table 3 Demographic and outcome variables in the analyzed responses and the excluded responses

Variables	The analyzed responses ($n = 32{,}223$)		The excluded responses ($n = 19{,}999$)		χ^2/ Mann–Whitney U[a]
	N/ Mean	%/ SD	*N*/ Mean	%/ SD	*p*
Gender					< 0.01
Men	8563	26.6%	4140	24.4%	
Women	23,619	73.3%	12,789	75.3%	
Other gender	41	0.1%	47	0.3%	
Missing	0		3023		
Age (years)	40.1	11.1	38.6	10.9	< 0.01
Occupation					< 0.01
Physicians	9119	28.3%	3958	28.3%	
Nurses	9323	28.9%	4818	34.4%	
Other healthcare workers[b]	6989	21.7%	2544	18.2%	
Ancillary workers[c]	3976	12.4%	1417	10.1%	
Other	2816	8.7%	1271	9.1%	
Missing	0		5991		
Contact with patients who had suspected or confirmed cases of COVID-19					< 0.01
No	10,516	32.6%	3898	28.4%	
Yes	16,065	49.9%	7770	56.5%	
I do not know	5642	17.5%	2079	15.1%	
Missing	0		6252		
History of mental health problems and drugs					0.03
No	27,369	84.9%	4194	85.6%	
Yes	4561	14.2%	677	13.8%	
I do not know	293	0.9%	27	0.6%	
Missing	0		15,101		
Country					< 0.01
Argentina	1483	4.6%	766	3.8%	
Armenia	292	0.9%	351	1.8%	
Belgium	0	0.0%	326	1.6%	
Bolivia	109	0.3%	58	0.3%	
Brazil	2377	7.4%	869	4.3%	
Chile	2982	9.3%	1131	5.7%	
Colombia	2437	7.6%	1459	7.3%	
Czech Republic	1344	4.2%	2324	11.6%	
Germany	159	0.5%	45	0.2%	
Guatemala	1265	3.9%	1087	5.4%	
Italy	4189	13.0%	1313	6.6%	
Japan	1078	3.3%	338	1.7%	
Lebanon	0	0.0%	768	3.8%	
Mexico	6476	20.1%	1792	9.0%	
Netherlands	407	1.3%	1320	6.6%	
Nigeria	273	0.8%	254	1.3%	
Peru	1351	4.2%	2403	12.0%	
Puerto Rico	0	0.0%	405	2.0%	
Saudi Arabia	118	0.4%	129	0.6%	
Spain	3204	9.9%	1168	5.8%	
Tunisia	458	1.4%	311	1.6%	
South Africa	0	0.0%	69	0.3%	
Uruguay	1629	5.1%	867	4.3%	

Table 3 (continued)

Variables	The analyzed responses ($n = 32{,}223$)		The excluded responses ($n = 19{,}999$)		χ^2/ Mann–Whitney *U*[a]
	N/ Mean	%/ SD	*N*/ Mean	%/ SD	*p*
Venezuela	592	1.8%	446	2.2%	
Missing	0		0		
PHQ-9 (range 0–27)	6.0	5.5	6.0	5.5	0.12
Incidence rate of COVID-19[d]	11.9	16.5	22.6	27.7	< 0.01
Mortality rate of COVID-19[e]	6.5	5.0	5.7	5.1	< 0.01

SD standard deviation, *COVID-19* novel coronavirus disease 2019, *PHQ-9* Patient Health Questionnaire-9

[a] Mann–Whitney *U* tests was conducted for continuous variables and Pearson's chi-square tests for categorical variables

[b] Other healthcare workers: e.g., psychologist, social worker, radiology technician, laboratory technician, physical therapist, respiratory therapist, dietician, dentist, occupational therapist, speech therapist, first responder (Paramedic/EMT), clinical manager/director, social-community mental health worker

[c] Ancillary HCWs: e.g., non-clinical manager, administrator/secretary/admission, patient transportation, food/hospitality, cleaning staff, maintenance staff, security staff

[d] Mean of incidence rate from 7 days before to the day before the survey day in the participants' country. The incidence rate was calculated as the number of cases per 100,000 population

[e] Mean of mortality rate from 7 days before to the day before the survey day in the participants' country. The mortality rate was calculated by dividing the number of recorded deaths by the number of cases and then multiplying by 100 to obtain a percentage

Table 4 Association between incidence rate of COVID-19[a] and depressive symptoms: results of multilevel linear mixed model ($N = 32{,}223$)

	Model 1 (Null model)			Model 2 (Crude model)			Model 3		
	Coefficient	SE	*p*	Coefficient	SE	*p*	Coefficient	SE	*p*
Fixed effect									
Intercept	6.444	0.368	< 0.001	6.442	0.356	< 0.001	4.041	0.279	< 0.001
Time (days)	−0.003	0.000	< 0.001	−0.003	0.000	< 0.001	−0.003	0.000	< 0.001
Variables									
Incidence rate of COVID-19[a] (cases/100,000)				0.011	0.003	< 0.001	0.008	0.003	0.003
Age (years)							−0.060	0.003	< 0.001
Gender: women (Ref: men)							1.147	0.065	< 0.001
Gender: other gender (Ref: men)							1.397	0.773	0.071
Occupation: nurses (Ref: physicians)							0.183	0.076	0.016
Occupation: other healthcare workers (Ref: physicians)							−0.423	0.081	< 0.001
Occupation: ancillary workers (Ref: physicians)							0.111	0.098	0.255
Occupation: other (Ref: physicians)							0.215	0.110	0.050
Contact with patients who had suspected or confirmed cases of COVID-19: yes (Ref: no)							1.415	0.068	< 0.001
Contact with patients who had suspected or confirmed cases of COVID-19: I do not know (Ref: no)							1.197	0.083	< 0.001
History of mental health problems: yes (Ref: no)							4.459	0.082	< 0.001
History of mental health problems: I do not know (Ref: no)							3.179	0.291	< 0.001
Random effect									
Intercept	2.506	0.828	0.002	2.330	0.772	0.003	1.261	0.425	0.003
Residual variance	27.944	0.220	< 0.001	27.993	0.220	< 0.001	24.340	0.192	< 0.001
AIC	198,859.363			198,854.551			194,434.531		

SE standard error

[a] Mean of incidence rate from 7 days before to the day before the survey day in the participants' country

The incidence rate was calculated as the number of cases per 100,000 population

Table 5 Association between mortality rate of COVID-19[a] and depressive symptoms: results of multilevel linear mixed model (*N* = 32,223)

	Model 1 (Null model)			Model 2 (Crude model)			Model 3		
	Coefficient	SE	*p*	Coefficient	SE	*p*	Coefficient	SE	*p*
Fixed effect									
Intercept	6.444	0.368	< 0.001	5.891	0.410	< 0.001	3.689	0.324	< 0.001
Time (days)	− 0.003	0.000	< 0.001	− 0.002	0.000	< 0.001	− 0.002	0.000	< 0.001
Variables									
Mortality rate of COVID-19[a] (%)				0.076	0.022	< 0.001	0.049	0.020	0.017
Age (years)							− 0.060	0.003	< 0.001
Gender: women (Ref: men)							1.149	0.065	< 0.001
Gender: other gender (Ref: men)							1.407	0.773	0.069
Occupation: nurses (Ref: physicians)							0.159	0.077	0.037
Occupation: other healthcare workers (Ref: physicians)							− 0.429	0.081	< 0.001
Occupation: ancillary workers (Ref: physicians)							0.101	0.098	0.302
Occupation: other (Ref: physicians)							0.227	0.110	0.038
Contact with patients who had suspected or confirmed cases of COVID-19: yes (Ref: no)							1.424	0.068	< 0.001
Contact with patients who had suspected or confirmed cases of COVID-19: I do not know (Ref: no)							1.195	0.083	< 0.001
History of mental health problems: yes (Ref: no)							4.456	0.082	< 0.001
History of mental health problems: I do not know (Ref: no)							3.174	0.291	< 0.001
Random effect									
Intercept	2.506	0.828	0.002	2.650	0.877	0.003	1.373	0.462	0.003
Residual variance	27.944	0.220	< 0.001	27.934	0.220	< 0.001	24.341	0.192	< 0.001
AIC	198,859.363			198,853.314			194,433.259		

SE standard error

[a] Mean of mortality rate from 7 days before to the day before the survey day in the participants' country

In summary, subgroup analyses showed that as the incidence rate increased, depressive symptoms worsened among men, women, nurses, those who had contact with patients who had suspected or confirmed cases of COVID-19, those without a history of mental health problems, and those living in low-and-middle-income countries. Subgroup analyses also showed that as the mortality rate increased, depressive symptoms worsened among women, those who had contact with patients who had suspected or confirmed cases of COVID-19, those with a history of mental health problems and those living in both high-income and low-and-middle-income countries.

In a sensitivity analysis of 30,520 responses, there was a similarly significant positive association of incidence and mortality rates with depressive symptoms in the multilevel LMM (Additional file 1: Table S28 and Table S29).

Discussion

This study showed the association of prior week incidence and mortality rates with depressive symptoms over 2 years among HCWs in 20 countries during and after the COVID-19 outbreak. In addition, the association of the incidence and mortality rates with depressive symptoms varied by the country and individual characteristics of the participants.

This study found that the increased daily incidence rates were associated with worsened depressive symptoms among HCWs in 20 countries, including both high-income and low-and-middle-income countries, regardless of the country of residence. Table 3 shows that in the best-fitting model 3, an increase of 1 per 100,000 in the mean incidence of COVID-19 from 7 days to 1 day before the survey date in the healthcare worker's country of residence increased the value of PHQ-9 of the participant by 0.008. In the Netherlands on February 12, 2022, which had the highest incidence rate of COVID-19 of 731.31 during the study period in 20 countries, the PHQ-9 score was calculated to have increased by 5.85 compared to when the incidence rate was 0. These results suggest that although the coefficient was small at 0.008, a high incidence rate would result in a large increase in the PHQ-9 score, which may exceed the cutoff score of 10 for major depressive disorder, and that the incidence rate was a serious associated factor for depressive symptoms among healthcare workers during the COVID-19 pandemic. The association between incidence rate and depressive symptoms among HCWs during the COVID-19 pandemic was consistent with the previous longitudinal study conducted in New York [44]. This study adds to the findings of previous studies that the incidence rate of COVID-19 is associated with depressive symptoms among HCWs not only in a local region but also in 20 countries, including both high-income and low-and-middle-income countries, and that the association persists for as long as 2 years, not just in the early stages of the COVID-19 pandemic. Reasons for the association over 2 years include a higher workload with increased incidence of COVID-19 and exhaustion with a prolonged COVID-19 pandemic, combined with the sense of no longer being valued by organizations or even by patients in an understaffed environment during and after the COVID-19 pandemic [15].

This study showed an association between depressive symptoms and the mortality rate among multinational HCWs during the first 2 years of the COVID-19 pandemic in 20 countries. Table 4 shows that in the best-fitting model 3, an increase of 1% in the mean mortality rate from 7 days to 1 day before the survey date in the participant's country of residence increased the PHQ-9 score of the participant by 0.049. Some reasons for observing the association even 2 years after the start of the COVID-19 pandemic include moral injury, difficult clinical decisions regarding patients with COVID-19, and repeated traumatic experiences of patient deaths throughout the pandemic [64]. Therefore, this study suggested that mortality rate might be a long-term associated factor in the mental health of healthcare workers internationally during the COVID-19 pandemic.

This study showed a long-term association between the incidence and mortality rates and depressive symptoms and revealed depressive symptoms over time and when mental health support was needed for HCWs during and after the COVID-19 pandemic. The results of Model 1 in Table 3 and Table 4 show that the PHQ-9 score of a participant decreased by 0.002 from 6.444 with each passing day from January 1, 2020. Thus, considering only time, depressive symptoms among HCWs were worst in the early stages of the COVID-19 pandemic and gradually improved over time. In addition, this study showed that the increased daily incidence and mortality rates were associated with worsening depressive symptoms over 2 years. As it has been reported that future trajectories of the incidence and mortality rates can be simulated [65–67], this study's results are important in identifying periods of worsening depressive symptoms among HCWs during and after the COVID-19 pandemic. This study suggested that countermeasures for depressive symptoms were needed in any country at the beginning of the pandemic and at the times of an increase in the incidence and mortality rates during the 2 years from the beginning of the COVID-19 pandemic. Training on infectious diseases and training on mental health, such as psychological first aid, may be an effective countermeasure for healthcare workers before a pandemic begins or in the very early stages [68, 69]. Psychoeducational interventions (e.g., online stress reduction information, behavioral changes including exercise) and psychosocial interventions (e.g., "talk therapy," crisis lines), which have been reported to be effective in previous studies [70–73], may be beneficial to the mental health of health care workers as a countermeasure during a pandemic, especially when infection and mortality rates increase. It may also be important for the government and affiliated organizations such as hospitals to plan and implement programs and countermeasures for the mental health of healthcare workers during a pandemic. This study indicated the need for additional mental health care for healthcare workers when the incidence rate and mortality rate of COVID-19 increased during the pandemic and suggests that specific measures may be needed for those whose mental health is particularly affected by the increases. Based on the results of the subgroup analysis, when the incidence and mortality rates increased, mental health countermeasures were especially needed for HCWs who were women, nurses, those who had contact with suspected or confirmed cases of COVID-19, and those who lived in low-and-middle-income countries.

Furthermore, this study's results may be applicable during future outbreaks of emerging infectious diseases other than COVID-19. It may be helpful to implement mental health countermeasures for HCWs during potential new global health emergency crises, both at the beginning of an epidemic and at the time of an increase in the incidence and mortality rates of emerging infectious diseases. This study also suggested that during outbreaks of emerging infectious diseases other than COVID-19, it may be necessary to identify the characteristics of healthcare workers who are particularly affected in their mental health by the increases in the incidence rate and mortality rate and to implement specific countermeasures for these healthcare workers. In addition, there might have been benefits to the participants in this study, including the fact that they were able to assess their own mental health and the possibility that the results of this study could prevent or improve their mental health in the future.

Limitations

There are several limitations to this study. First, because this study was based on convenience sampling in most countries and recruitment methods differed somewhat from country to country, it is necessary to interpret the findings of this study with attention to the representativeness of the participants. Selection bias due to the methods used to recruit participants may have limited the generalizability of the results. Examples of selection bias could include the fact that the recruitment methods created biases in the medical specialties of the participants and the hospitals in which they worked, resulting in characteristics of the participants that differed from those of the general healthcare workforce during the COVID-19 pandemic. HCWs who experienced a severe worsening of depressive symptoms during the pandemic may not have been able to participate in this study because of severe depressive symptoms or because they had retired from their jobs. The mean PHQ-9 score for participants in this study was 6.0, and 14.2% had a history of mental health problems, indicating some inclusion of HCWs with worsening depressive symptoms, but selection bias may have occurred if those with severe depressive symptoms were unable to participate. Future studies are needed using recruitment methods that do not cause selection bias, such as random sampling. Second, many participants were excluded due to missing values in their responses. As most participants in this study responded only once and missing values in the present study should occur not at random, the implementation of missing value imputation, such as multiple imputation, was problematic and missing values could not be imputed. The bias in the characteristics of the excluded responses, such as incidence rate, mortality rate, demographic variables, and work-related variables, compared to the included responses in this study may have affected the results and could affect the generalizability of the findings. The exclusion of responses from all participants in all four countries due to missing values could affect the generalizability of the findings. To address this limitation, this study conducted several subgroup analyses to investigate the association between incidence and mortality rates and depressive symptoms by demographic variables such as gender, occupation, and high-income and low-and-middle-income countries. Third, because the study applied the incidence and mortality rates of COVID-19 for each country, the rates in the participant's region might have differed from those in their country if there were significant regional differences. In future studies, examining associations using national and regional level incidence and mortality rates of COVID-19 may provide further understanding of the association with mental health. Fourth, some factors that might have been related to the incidence and mortality rates of COVID-19 and depressive symptoms among HCWs during the COVID-19 pandemic could not be included in the model in the analysis. Although the incidence and mortality rates of COVID-19 were country-level factors, and thus confounding factors were unlikely in their association with depressive symptoms, the model in the analysis might have been more appropriate if variables such as vaccination against COVID-19, which could not be measured because the study was conducted before the development of the vaccine against COVID-19, could have been included [74]. Fifth, participants' response dates were scattered across approximately all days of the period, although some days had no one who had responded. Although we addressed this limitation by conducting the LMM analyses, it may have affected the results of this study. Sixth, this study examined the association between the incidence rate and mortality rate of COVID-19 and depressive symptoms with time by skillfully creating and analyzing the time variable. Still, the causality cannot be clarified due to the cross-sectional study design, and caution should be needed in interpreting the results. It would be useful to conduct a longitudinal study to investigate the long-term association between the incidence rate and mortality rate and the mental health of healthcare workers during a pandemic in the future. Finally, the ICC for the PHQ-9 was low among all responses of the analyzed participants, which means only 7% of the total variance in depressive symptoms was explained at the country level. The multilevel analysis of country and individual was appropriate because country differences in the random effect were significant in each of the LMM models. Still, factors related to the individual may explain more about HCWs' mental health during the COVID-19 pandemic than factors related to the country. However, it should be remembered that factors related to individuals also include social determinants of health.

Conclusions

This is the first study to show an association between depressive symptoms and the incidence and mortality rates of COVID-19 among multi-country HCWs during the first 2 years of the pandemic. This study indicates that additional mental health care for HCWs was needed when the incidence and mortality rates of COVID-19 were increasing during and after the early phase of the pandemic. In addition, the association of depressive symptoms with the incidence and mortality rates of COVID-19 varied by the country and individual characteristics of the participants. The study's findings may apply to future pandemics.

Abbreviations

AIC	Akaike Information Criteria
COVID-19	Novel coronavirus disease
HCWs	Healthcare workers
HEROES study	COVID-19 HEalth caRe wOrkErS study
ICC	Intraclass correlation coefficients
IRBs	Institutional Review Boards
LMM	Linear mixed models
PHQ-9	Patient Health Questionnaire-9
REDCap	Research Electronic Data Capture
ReML	Restricted maximum likelihood
SD	Standard deviation
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03585-8.

Additional file 1: FigureS1, S2- [Trends in the mean of the incidence and mortality rates in each country]. Table S1- [Number of responses in each month for each country]. Table S2-S29- [Results of multilevel LMMs were conducted in each of the subgroups classified by gender, occupation, contact with patients who had suspected or confirmed cases of COVID-19, history of mental health problems, and high-income and low-and-middle-income countries]. Table S30- [The members of the HEROES study group].

Acknowledgements

The members of the HEROES study group were listed in Table S30. We also acknowledge all HCWs, all hospitals, and healthcare institutions that participated in the survey.

Authors' contributions

HA had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: HA, KW, YM, DN. Acquisition, analysis, or interpretation of data: HA, KW, YM, AR, EV, MF, LA, OA, AB1. AB2, SD, ME, EF, FF, LG, HH, RE, JL, HM, GM, RM, CM, JN, UO, AB3, EC, JR, AM, DS, AT, LV, OG, DB, MG, AI, AJ, JS, MT, RA, ES, FM, DN. Drafting of the manuscript: HA, KW, YM, MF, DN. Critical review of the manuscript for important intellectual content: HA, KW, YM, AR, EV, MF, LA, OA, AB1. AB2, SD, ME, EF, FF, LG, HH, RE, JL, HM, GM, RM, CM, JN, UO, AB3, EC, JR, AM, DS, AT, LV, OG, DB, MG, AI, AJ, JS, MT, RA, ES, FM, DN. Statistical analysis: HA, KW, DN. Obtained funding: HA, DN. Administrative, technical, or material support: HA, DN. Supervision: DN. All authors read and approved the final manuscript.

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Availability of data and materials

The dataset and statistical/analytical code that support the findings of this study are available from the corresponding author, D.N., upon reasonable request. The dataset is not publicly available due to privacy reasons.

Data Availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by accredited Institutional Review Boards (IRBs) in each participating country, including the IRB of the Faculty of Medicine, University of Chile; Columbia University Medical Center IRB; Hospital La Paz Ethics Committee; Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine at the University of Tokyo (No. 2019164NI-(1)(2)(3)(4)) and the research ethics committee of the National Hospital Organization Disaster Medical Center (No. 2019–19) in Japan; National Committee of Ethics in Research (CONEP/CNS/MS); Ethics Committee of the Azienda Mista Ospedaliero-Universitaria of Cagliari; University of Ibadan/University College Hospital Ethics Review Committee; Instituto Jalisciense de Salud Mental (SALME); Comité de Ética de Investigación en Seres Humanos, de la Facultad de Medicina, Universidad de Chile; IRB University of Applied Sciences Emden / Leer; Comité de Bioética, de la Facultad de Medicina, Universidad Mayor de San Simón; Ponce Health Sciences University; Ethics Committee of the Czech Ministry of Health, Ethics Committee at the Second Faculty of Medicine, Charles University in Prague; Institutional Ethics Committee at the Institute of Molecular Biology of National Academy of Sciences of Armenia; King Abdullah International Medical Research Center (KAIMRC) IRB committee; Comité de Bioética en Investigación en Salud, Universidad de San Carlos de Guatemala; Bioethics Committee of the National School of Public Health, University of Antioquia and Pan-American Health Organization Ethics Review Committee. In the Netherlands, ethical approval was waived by the Medical Ethical boards of the Maastricht University Medical Center and the Amsterdam Medical Center, because the participants were not regarded as patients or identifiable persons sharing sensitive information following the Medical Research Involving Human Subjects Act (WMO). All participants provided informed consent to participate.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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