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Assessing and evaluating the impact of the covid 19 pandemic on anxiety and stress: A global perspective

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Assessing and evaluating the impact of the covid 19 pandemic on anxiety and stress: A global perspective

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Determinants of Poor Sleep Quality During the COVID-19 Pandemic Among Women Attending Antenatal Care Services at the Health Facilities of Debre Berhan Town, Ethiopia: An Institutional-Based Cross-Sectional Study

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Background: Women's ability to get sleep can be affected by pregnancy-related hormonal changes or other external stressful situations like the coronavirus disease 2019 (COVID-19).

Objective: The objective of this study was to assess the proportion of poor sleep quality during the COVID-19 pandemic and its determinants among pregnant women attending antenatal care (ANC) services.

Methods: An institutional-based cross-sectional study was conducted among 423 women attending ANC services at the health facilities in Debre Berhan Town, Ethiopia, from May to June 2020. A systematic random sampling technique was used to select the required samples. The tool consisted of questions that assessed (1) socio-demographic characteristics, obstetric and health care service-related characteristics; and media exposure to get information regarding COVID-19 infection; (2) To assess sleep quality; the Pittsburgh Sleep Quality Index (PSQI) was applied. And a global score of >5 indicates poor sleep quality, and a global score of ≤ 5 indicates good sleep quality.

Result: The overall prevalence of poor sleep quality was 62.8%, and was associated with pregnant women aged ≥ 46 years (AOR = 4.27), being in the third trimester (AOR = 2.51), being multigravida (AOR = 2.72), and having co-morbidity (AOR = 3.57).

Conclusion: The prevalence of poor sleep quality among pregnant women during the pandemic was found to be high. Advanced maternal age, third trimester pregnancy, being multigravida, and having comorbidity were determinants of poor sleep quality among pregnant women during the COVID-19 pandemic.

Keywords: COVID-19, sleep quality, women, Ethiopia, pregnancy

BACKGROUND

Pregnancy is a process accompanied by dramatic hormonal changes (1–3) that create significant anatomical, physiological, and biochemical changes in a woman's life. These hormonal changes can also have profound effects on women's ability to sleep and may result in poor sleep quality (4–7). Sleep is a physiological process and a basic requirement for the physical and mental well-being of pregnant women and their fetuses (2, 8). Furthermore, sleep disturbances and short sleep duration are common during pregnancy (9, 10), which can have an impact on health-related quality of life. Although a sleep problem may start soon after conception, it worsens in frequency and duration as the pregnancy advances more (11).

Sleep has a critical role in promoting the health of both the mother and the fetus (12). Worldwide, approximately one-third of all pregnant women reported that they had disturbed sleep during pregnancy (13). Disturbed sleep during pregnancy is linked to several complications, including preeclampsia, premature birth, gestational diabetes, postpartum depression, and intrauterine growth retardation (9, 13). Studies in different areas of the world reported that the prevalence of poor sleep quality among pregnant women was 17% in Peru (14), 41.2% in Vietnam (15), 43.1% in the Asian population (4), 45.7% in Canada (16), 51.8–87% in China (10, 11), 53.3% in Pakistan (17), 59.5% in Indonesia (18), 73% in the United States (1). Some studies showed the prevalence of poor sleep quality among pregnant women before the pandemic in Ethiopia at Jimma medical center 30.8% (8) and Wadila primary hospital 68.4% (2).

The determinants of poor sleep quality among pregnant women significantly varied with the trimester of the pregnancy. Overall, poor sleep quality had a direct correlation with advanced age, maternal education level, being unmarried, anxiety, depression, stress, gestational age, multiparous, multigravida, and watching television in the bedroom (2, 8, 10, 11, 15, 18). In addition, there are also many external stressful situations, like the coronavirus disease 2019 (COVID-19), which can result in disturbed sleep during pregnancy.

Studies reported that COVID-19 harmed sleep quality in the general populations (19–21). This problem may become worsen in pregnant women. The global pandemic COVID-19 infection has been shown to have an important impact on pregnant women and their fetuses. Pregnant women may experience fear of contracting COVID-19 (22) and its consequences, which can result in anxiety, depression, stress, and insomnia (23, 24). Additionally, pregnant women encountered partial immune suppression and became more susceptible to COVID-19 infection during the pandemic (25). All of this can lead to the development of negative emotions and cause pregnant women to be more concerned about the COVID-19 infection, resulting in sleep disruption (12) and poor sleep quality (26).

COVID-19 related morbidity and mortality are shockingly increasing in Ethiopia. This phenomenon may create stressful situations, especially for those at high risk, like pregnant women. Consequently, this COVID-19-related negative emotion among pregnant women could result in difficulty in getting sleep. However, there are limited studies done regarding sleep quality among pregnant women during the COVID-19 pandemic in Ethiopia. So, this study aimed to assess the prevalence of poor sleep quality and its determinant factors among pregnant women attending antenatal care (ANC) services during the era of the COVID-19 pandemic at Debre Berhan Town, Ethiopia in 2020.

MATERIALS AND METHODS

Participants and Procedure

An institutional-based cross-sectional study was conducted from May 1 to June 1, 2020, in Debre Berhan Town public health institutions. The source populations for the study were all pregnant women who are attending antenatal care services in Debre Berhan town. All pregnant women who are attending antenatal care services in the Town during the study period and fulfill the inclusion criteria were included as the study population. The sample size was determined by using the single population proportion formula with the assumption of 50% poor sleep quality, a 95% confidence interval, and a 5% marginal error. After adding a 10% non-response rate, the final sample size was 423. In this study, pregnant women who visited the public health institutions in Debre Berhan Town for ANC services were included in the study. And pregnant women who were unable to communicate effectively due to serious illness were excluded from the study. To select our study participants, all public health facilities in Debre Berhan town were considered, and then based on the number of pregnant women that visited the public health facilities during the preceding month before data collection, proportional allocation of the total sample size was carried out to get the required sample from each public health facility. Finally, the determined samples were selected with a mean age of 28 years (SD $\pm$ 4.86) by a systematic random sampling technique.

Data Collection Tools and Procedures

Pretested and interviewer-administered questionnaires were used for the whole survey. The tool consisted of 33 items categorized in to two sections, (1) socio-demographic characteristics, obstetric and health care service-related characteristics; and media exposure to get information regarding COVID-19 infection with a total of 14 items; (2) items to assess sleep quality by the Pittsburgh Sleep Quality Index (PSQI). The Pittsburgh Sleep Quality Index contains 19 Likert-type and open-ended questions. Respondents were asked about their overall sleep quality and how frequently they had experienced certain sleep difficulties in the previous month. The 19 items were combined to form seven component scores, each of which had a range of 0–3, with a higher score indicating more acute sleep disturbances. Then, the seven component scores were added to yield a single global score ranging from 0 to 21, with the higher score indicating severe sleep difficulties in all areas. PSQI developers have suggested a cutoff score of 5 for the global scale as it was 88.5% valid to correctly identify the problem (27–29). The Cronbach alpha of PSQI in the current study was 0.72. Furthermore, the data was collected by trained BSc midwives, and the consistency and completeness of the data were checked daily by supervisors.

Variable of Interest

Sleep Quality

Is defined based on the PSQI score; hence, a global score of >5 indicates poor sleep quality, and a global score of ≤5 indicates good sleep quality (27).

Exposure to the Media

Women who had access to either television, radio, or read newspapers at least once a week was considered exposed to the media.

Co-morbid Disease

Is defined as the co-existence of diagnosed chronic medical conditions like asthma, diabetes mellitus, heart disease, hypertension, depression, cancer, and chronic kidney disease among pregnant women (30).

Statistical Analysis

The data was first entered into EPI INFO^{TM} 7 and then exported to STATA version 14, statistical software for analysis. Frequencies and cross-tabulations were applied to summarize descriptive statistics of the data, and tables were used for data presentation. A binary logistic regression model was used to identify factors associated with poor sleep quality. Those variables with a *p*-value less than or equal to 0.2 from the bi-variable analysis were candidates for multivariable analysis. Variables with a *p*-value of less than 0.05 in multivariable analysis were declared as statistically significant factors for poor sleep quality. Moreover, the association was measured using odds ratios with a 95% confidence interval. Model fitness was also checked by the Hosmer-Lemeshow goodness of fit test (*P*-value = 0.491).

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board (IRB) of Debre Berhan University and an official permission letter was gained from the concerned body. Written informed consent was obtained from each participant before conducting the actual data collection process. Additionally, confidentiality was maintained by avoiding registration of personal identifiers and no raw data was given to anyone other than the investigator.

RESULTS

Pregnant Women's Socio-Demographic, Obstetric, and Healthcare-Related Characteristics

Of the 423 pregnant women, almost all (99.8%) participated in the analysis. Of these, 175 (41.47%) were found under the category of age 25 years or less, with a mean age of 28 years (SD ± 4.86). The majority (86.73%) of the participants were married, and 164 (38.86%) of the women had primary education levels. Of all the participants included in the analysis, 241 (57.11%) were housewives. About one-third (34.36%) of the participants' husbands were at the primary education level, and 216 (51.18%) of their husbands were merchants. One hundred ninety-four (46%) pregnant women lived 2–5 km away from the health facility. Similarly, more than half (54.5%) of the participants were in the third trimester and 250 (59.24%) were multi-gravida. On the other hand, the majority of the women (89.8%) had no known co-morbid diseases. Around 81.5 and 57.4% of the women watched television and heard the radio to get information, including COVID-19, respectively. But, the majority of the women (90.52%) didn't have the habit of reading newspapers during the era of the pandemic (**Table 1**).

TABLE 1 | The socio-demographic and obstetric-related characteristics of pregnant women attending antenatal care (ANC) services in Debre Berhan (*n* = 422).

Variable	Categories	Frequency	Percentage (%)
Maternal age	<25 years	175	41.47
	26–35 years	67	15.88
	36–45 years	108	25.59
	≥46 years	72	17.06
Marital status	Single	27	6.40
	Married	366	86.73
	Divorced	29	6.87
Maternal education	No formal education	138	32.70
	1^0 education	164	38.86
	2^0 education	59	13.98
	Diploma and above	61	14.45
Maternal occupation	Housewife	241	57.11
	Government employee	73	17.30
	Private employee	60	14.22
	Student	48	11.37
Husband education	No formal education	94	22.27
	1^0 education	145	34.36
	2^0 education	94	22.27
	Diploma and above	89	21.09
Husband occupation	Employed	163	38.63
	Merchant	216	51.18
	Daily labor	43	10.19
Number of persons living with her	≤4 individual	339	80.33
	>4 individuals	83	19.67
Distance to the health facility	<2 km	192	45.50
	2 – 5 km	194	45.97
	>5 km	36	8.53
Trimester of pregnancy	1st trimester	63	14.93
	2nd trimester	129	30.57
	3rd trimester	230	54.50
Gravidity	Primigravida	172	40.76
	Multigravida	250	59.24
Co-morbid disease	Present	43	10.19
	Absent	379	89.81
Watch TV before bedtime	Yes	344	81.52
	No	78	18.48
Heard the radio before bedtime	Yes	242	57.35
	No	180	42.65
Ever read a newspaper about COVID-19	Yes	40	9.48
	No	382	90.52

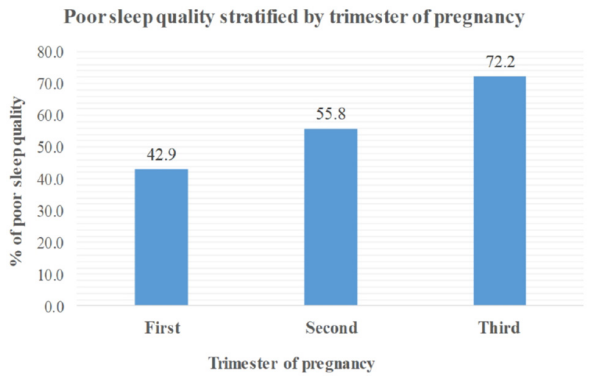

FIGURE 1 | Poor sleep quality among pregnant women stratified by trimester at Debre Berhan town, Ethiopia, 2020.

The Prevalence of Poor Sleep Quality Among Pregnant Women

The overall prevalence of poor sleep quality among pregnant women attending ANC service at health facilities in Debre Berhan town was 62.8% (95% CI: 58.1–67.3). The prevalence of poor sleep quality among pregnant women increases with gestational age, showing the highest proportion in the third trimester (**Figure 1**).

Determinants of Poor Sleep Quality Among Pregnant Women

After applying multivariable binary logistic regression, four variables, namely maternal age, trimester of pregnancy, gravidity, and presence of co-morbidity, were significantly associated with poor sleep quality among pregnant women. Thus, the odds of having poor sleep quality among pregnant women aged ≥46 years was 4.27 times that of women aged less than 25 years [AOR = 4.27; 95% CI: 1.43–12.79]. Similarly, the likelihood of experiencing poor sleep quality was 2.51 times higher in the third trimester compared to the first trimester [AOR = 2.51; 95% CI: 1.175–42]. Likewise, multigravida women were 2.72 times more likely than primigravida women to have poor sleep quality [AOR = 2.72; 95% CI: 1.34–5.50]. Pregnant women with the co-morbid disease were 3.57 times more likely to have poor sleep quality than pregnant women without comorbidity [AOR = 3.57; 95% CI: 1.45–8.78] (**Table 2**).

DISCUSSION

In this study, the overall magnitude of poor sleep quality among pregnant women during the era of COVID-19 was 62.8% (95% CI: 58.1–67.3). This is in line with studies conducted in Indonesia (59.5%) (18) and Northern Ethiopia (68.4%) (2). But, the magnitude of poor sleep quality in the current study was lower than in studies conducted in Turkey (88%) (26), China (87%) (11), and the United States (73%) (1). The discrepancy might be due to differences in socio-demographic characteristics and in the time when the study was conducted. On the other hand, poor sleep quality in the current study was higher than in studies from Peru, China, Pakistan, Vietnam, the Asian population, and Canada, ranging from 17 to 53.3% (4, 10, 14–17, 31, 32). The majority of these previous studies were conducted before the outbreak of the global COVID-19 pandemic, so the women couldn't worry about the infection compared to the women in the current study. Furthermore, being quarantined and apart from loved ones during the COVID-19 pandemic might increase the proportion of depressive symptoms, stress, and anxiety. These psychological situations in turn affect the sleep quality of pregnant women (18, 33).

The odds of having poor sleep quality were 4.27 times higher in pregnant women aged 46 years and older than in women aged less than 25 years. This is supported by studies from China (11), and Ethiopia (2, 8). As maternal age increases, the likelihood of women being affected by physiological and psychological factors will also increase (34). This might in turn result in poor sleep quality (35).

Similarly, a significant association between gestational age and sleep quality was detected, showing that sleep quality declines as pregnancy advances. Hence, the risk of developing poor sleep quality among pregnant women in the third trimester was 2.51 times greater than that of pregnant women in the first trimester. This is consistent with studies from China (10, 11), Turkey (36), and Ethiopia (2). As gestational age increases, the tendency for frequent urination, even at night, increases and results in disturbed sleep (37). Additionally, when the woman approaches her end date of delivery, she might worry about childbirth, finance, labor, and delivery, or the baby's health, which all could be risk factors for disturbed sleep (37, 38). Weight gain, along with hormonal and physiological changes, induces pregnant women to have sleep-disordered breathing like snoring and obstructive sleep apnea, which in turn disturbs the normal sleep pattern (38).

A significant association between gravidity and sleep quality was discovered, showing that sleep quality declines as the number of pregnancies increases. When compared to primigravida, the likelihood of having poor sleep quality was 2.72 times among women with multigravida. This is consistent with research on pregnant women in Jimma, Ethiopia (8), and South Korea (39). This may be explained by the fact that maternal sleep quality is disturbed as a result of being overstressed about bearing extra roles after childbirth and the way they integrate the new role into their pre-existing responsibilities. Excessive worry caused by rehearsing physical pain during labor and delivery may also contribute to poor sleep quality in multigravida women (39).

Lastly, the presence of co-morbid disease among pregnant women was found to be significantly associated with poor sleep quality. Hence, pregnant women with co-morbid disease were 3.57 times more likely to develop poor sleep quality compared to pregnant women without comorbidity. This is supported by studies from Indonesia and the United States which declared that depression and gestational diabetes mellitus were directly associated with poor sleep quality (1, 18), respectively. This could be a reason for extra worry among pregnant women with medical comorbidity, which might induce a disturbed sleep pattern. Additionally, fear of a bad outcome for her baby and her as a

TABLE 2 | Bivariate and multivariate sleep quality analysis among pregnant women in Debre Berhan (n = 422).

Variable	Category	Sleep quality		COR (95%CI)	AOR (95%CI)	*P*-value
		Good	Poor			
Maternal age	<25 years	88	87	1.00	1.00	
	26–35 years	17	50	2.97 (1.59–5.56)*	1.91 (0.77–4.72)	0.160
	36–45 years	40	68	1.72 (1.05–2.81)*	1.28 (0.61–2.70)	0.519
	≥46 years	12	60	5.06 (2.54–10.05)*	4.27 (1.43–12.79)	0.009**
Marital status	Single	9	18	1.00	1.00	
	Married	143	223	0.78 (0.34–1.78)	0.42 (0.13–1.34)	0.142
	Divorced	5	24	2.39 (0.69–8.39)*	2.14 (0.46–9.91)	0.333
Maternal education	No formal education	44	94	1.04 (0.55–1.98)	2.28 (0.94–5.52)	0.067
	1^0 education	69	95	0.67 (0.36–1.25)*	1.36 (0.59–3.13)	0.476
	2^0 education	24	35	0.71 (0.34–1.49)	1.78 (0.66–4.77)	0.254
	Diploma and above	20	41	1.00	1.00	
Maternal occupation	Housewife	97	144	1.00	1.00	
	Government employee	23	50	1.46 (0.84–2.56)*	1.19 (0.56–2.53)	0.651
	Private employee	14	46	2.21 (1.15–4.25)*	2.03 (0.92–4.48)	0.079
	Student	23	25	0.73 (0.39–1.36)	2.18 (0.81–5.81)	0.121
Husband education	No formal education	36	58	0.74 (0.40–1.36)	0.92 (0.34–2.47)	0.872
	1^0 education	58	87	0.69 (0.39–1.20)*	0.88 (0.38–2.07)	0.773
	2^0 education	35	59	0.77 (0.42–1.43)	0.87 (0.33–2.26)	0.769
	Diploma and above	28	61	1.00	1.00	
Husband occupation	Employed	58	105	1.00	1.00	
	Merchant	77	139	0.99 (0.65–1.54)	1.21 (0.57–2.57)	0.615
	Daily labor	22	21	0.53 (0.27–1.04)*	0.56 (0.20–1.56)	0.269
No. of people living with	≤4 individual	132	207	1.00	1.00	
	>4 individuals	25	58	1.48 (0.88–2.48)*	0.58 (0.29–1.16)	0.125
Distance to the health facility	<2 km	78	114	1.00	1.00	
	2 – 5 km	66	128	1.33 (0.88–2.01)*	0.92 (0.52–1.63)	0.780
	>5 km	13	23	1.21 (0.58–2.53)	0.46 (0.15–1.39)	0.171
Trimester of pregnancy	1st trimester	36	27	1.00	1.00	
	2nd trimester	57	72	1.68 (0.92–3.09)*	1.31 (0.55–3.14)	0.542
	3rd trimester	64	166	3.46 (1.94–6.15)*	2.51 (1.17–5.42)	0.019**
Gravidity	Primigravida	91	81	1.00	1.00	
	Multigravida	66	184	3.13 (2.08–4.72)*	2.72 (1.34–5.50)	0.006**
Co-morbid disease	Present	7	36	3.37 (1.46–7.77)*	3.57 (1.45–8.78)	0.006**
	Absent	150	229	1.00	1.00	
Watch TV before bedtime	Yes	123	221	1.39 (0.84–2.29)*	1.85 (0.79–4.36)	0.158
	No	34	44	1.00	1.00	
Heard the radio before bedtime	Yes	83	159	1.34 (0.89–1.99)*	1.12 (0.59–2.12)	0.713
	No	74	106	1.00	1.00	
Read newspaper about COVID-19	Yes	16	24	0.88 (0.45–1.71)		
	No	141	241	1.00		

**Candidate variables for multivariate analysis at p-value ≤ 0.2. **Statistically significant factors at a p-value of <0.05.*

result of existing comorbidity may contribute to the occurrence of poor sleep quality.

CONCLUSION

Nearly two-thirds of pregnant women in this study had poor sleep quality. Women with advanced age, being in the third trimester, multigravida, and comorbidity were associated with poor sleep quality among pregnant women. Giving special attention to women of advanced age, third trimester pregnancy, multigravida, and counseling of the women with comorbidity in their consecutive antenatal care visits is crucial to reduce the risk of developing poor sleep quality and its consequences.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Debre Berhan University College of Health Science research committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NA conceived the idea, designed the work, and collected the data. BC collected the data and participated in the manuscript writing. AA analyzed the data, interpreted the results, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Prevalence and Associated Factors of Depression, Anxiety and Insomnia Symptoms Among Patients Receiving Ophthalmic Consultation Online During the COVID-2019 Pandemic

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Objective: This study aims to assess the prevalence and associated factors of depression, anxiety and insomnia symptoms among patients undergoing ophthalmic consultation online during the coronavirus disease 2019 (COVID-2019) pandemic.

Methods: We reviewed the data of patients who received online ophthalmic consultations during the lockdown period from February to August 2020, and an online survey was conducted among them. We collected the respondents' demographic data and their attitudes toward the online consultation, assessed the depression, anxiety and insomnia symptoms and estimated associated factors by logistic regression analysis.

Results: The online service provided 425 consultations during the COVID-19 lockdown period. Of these eligible subjects, 139 patients responded to an invitation to participant in the study (105/75.5% were females, and 40/28.8% were health care workers). More than half of the participants reported that they trusted and were satisfied with the online consultation (109/78.4% and 82/59%, respectively). Fifty-two (37.4%), 32 (23.0%), and 53 (38.1%) patients showed symptoms of depression, anxiety, and insomnia, respectively. Depression was found to be significantly more common in health care workers ($P = 0.019$) and those who were basically satisfied with online consultation ($P = 0.024$). Anxiety was more common among participants who had used electronics for a long time ($P = 0.038$). Binary logistic regression showed health care work as a risk factor for depressive symptoms (odds ratio [OR]: 2.424; 95% CI: 1.143–5.143; $P = 0.021$).

Conclusion: Psychological distress is highly prevalent among patients who were involved in online consultation for ocular manifestations during the COVID-19 lockdown period. In the context of a major public health event, ophthalmologists should focus not only on ocular symptoms but also on the mental health of their patients, and appropriate psychological support should be given.

Keywords: coronavirus disease 2019, ophthalmic online consultation, patients, depression, anxiety, insomnia

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a public health emergency of international concern, according to a World Health Organization declaration on January 31, 2020 (1, 2). Since the start of the pandemic, there have been over 370 million reported cases and over 5.6 million deaths globally according to February 1, 2022, data from the WHO (3).

The rapid spread of the disease via close contact between people is an important feature of COVID-19 (4). It has prompted precautions in public places, such as hospitals, which are prone to transmission of communicable diseases due to the large number of people congregating in confined spaces. To curb the spread of the disease, compulsory measures were being implemented by governments, such as social distancing, isolation/lockdowns, and social activity restrictions) (5, 6). These restrictions have brought about great changes in people's life. Firstly, non-COVID-19 patients' medical needs have been greatly affected, which may have caused psychological distress. However, the emergence of a virtual hospital, not limited by place or time that enabled patients to see physicians while avoiding a crowded waiting room, became an alternative for many patients (7). Online consultation can address some patients' needs, but it is uncertain whether seeing a health care provider virtually can affect patients' mental state. Secondly, measures of remote working were also being imposed in many organizations. Coupled with home quarantine, there had been a marked decrease in outdoor activity and an increase in screen time, which had been shown to be associated with mental health problems (8).

Some studies have investigated the psychological impact related to the COVID-19 crisis on people. One online survey of 56,679 individuals from all 34 provincial-level regions in China showed that 27.9% of respondents reported depression, 31.6% anxiety, 29.2% insomnia, and 24.4% acute stress, as evaluated by the Patient Health Questionnaire-9, Generalized Anxiety Disorder-7, Insomnia Severity Index, and Acute Stress Disorder Scale (9). Another survey of medical staff found rates of anxiety and depressive symptoms were 13.3 and 18.4%, respectively (10). However, there are few studies on the psychological status of patients, especially those who consult with ophthalmologists online.

This study collected the consultation information of ophthalmic patients at the "online hospital" and conducted an online psychological questionnaire survey with the aim of assessing ophthalmic patients' symptoms of depression, anxiety, and insomnia, as well as analyzing potential associated factors with these symptoms during COVID-19 lockdown to provide a basis for interventions in public health emergencies.

METHODS

Data (including name, sex, and consultation content) of patients receiving online ophthalmology consultation during the lockdown period (from February 15, 2020 to August 14, 2020) were collected through the online consultation platform of People's Hospital of Xinjiang Uygur Autonomous Region. We divided the patient consultation content into 12 sections: blurred or different vision, eye discomfort or abnormal appearance, fluttering shadows before eyes, myopia and abnormal eye position, outpatient follow-up and further treatment, and abnormal secretions, ocular trauma, eye surgery, postoperative follow-up, invalid consultations such as just saying hello without describing any symptoms or describing conditions that have nothing to do with ophthalmology, repeated consultations, and other such as asking about medication usage, whether medication can be delivered by express delivery, the cost of certain tests and the availability of doctors for work.

The subjects of this study were the aforementioned patients who underwent online ophthalmic consultations during the COVID-19 lockdown. We sent questionnaires online to these people through Wenjuanxing, a survey platform in China. The first part of the online questionnaire recorded basic information about the participants (including name, sex, age, education level, whether they were medical workers, current status, whether they had used electronic products for a long time). The second part of the questionnaire involved the use of three tools to assess patients' symptoms of depression, anxiety, and insomnia, respectively: the Chinese versions of the nine-Item Patient Health Questionnaire (PHQ-9) (11), the seven-item Generalized Anxiety Disorder scale (GAD-7) (12) and the seven-item Insomnia Severity Index (ISI) (13). The last part of the questionnaire surveyed participants' trust in and satisfaction with online counseling. These measurement tools were scored as follows: PHQ-9, normal (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27) depression; GAD-7, normal (0–4), mild (5–9), moderate (10–14), and severe (15–21) anxiety; ISI, normal (0–7), subthreshold (8–14), moderate (15–21), and severe (22–28) insomnia.

This study was a cross-sectional online survey conducted from August 16 to August 29, 2020, which was approved by the Ethics Committee of Zhongshan Ophthalmic Center, Sun Yat-sen University, and People's Hospital of Xinjiang Uygur Autonomous Region. Written informed consent was received online from all participants before the study.

STATISTICAL ANALYSIS

Data were described as frequencies and percentages. We used the Shapiro–Wilk test to determine that the scale scores did not conform to a normal distribution and presented data as medians with interquartile ranges (IQRs). Chi-square and Fisher's exact tests were used to compare the socio-demographic differences between those with depression vs. those without depression, those with anxiety vs. those without anxiety and those with insomnia vs. those without insomnia, respectively. A binary logistic regression analysis was established to determine the risk factors for depression, anxiety, and insomnia symptoms, and outcomes were presented as odds ratios (ORs) and 95% CIs. The significance level was $P = 0.05$ at a 2-tailed. Data were analyzed using SPSS version 22.0.

TABLE 1 | The content and proportion of online consultation.

Consultation Content	Epidemic period, No. (%)
Abnormal secretions	11 (2.6)
Blurred or different vision	20 (4.7)
Eye discomfort or abnormal appearance	165 (38.8)
Fluttering shadows before eyes	5 (1.2)
Myopia and abnormal eye position	13 (3.1)
Ocular trauma	5 (1.2)
Eye surgery	28 (6.6)
Outpatient follow-up and further treatment	22 (5.2)
Postoperative follow-up	12 (2.8)
The other	16 (3.8)
Invalid consultations	14 (3.3)
Repeated consultations	114 (26.8)

TABLE 2 | Socio-demographic variables of participants.

Variables	Participants, No. (%)
Overall	139 (100.0)
Gender	
Male	34 (24.5)
Female	105 (75.5)
Age	
<18	5 (3.6)
18–25	27 (19.4)
26–30	27 (19.4)
31–40	47 (33.8)
41–50	24 (17.3)
51–60	5 (3.6)
>60	4 (2.9)
Ethnic group	
Han	111 (79.9)
Minorities	28 (20.1)
Level of education	
Elementary School	7 (5.0)
Junior High School	6 (4.3)
Senior High School	20 (14.4)
Bachelor	91 (65.5)
Master	10 (7.2)
Doctor	5 (3.6)
Are you a healthcare worker?	
Yes	40 (28.8)
No	99 (71.2)
Current status	
Staying at home	100 (71.9)
Working outside	399 (28.1)
Do you use electronics for a long time?	
Yes	126 (90.6)
No	13 (9.4)
Sense of trust in online consultation	
Trust	109 (78.4)
Distrust	2 (1.4)
Unsure	28 (20.1)
Satisfaction toward online consultation	
Satisfied	82 (59.0)
Basically satisfied	32 (23.0)
Dissatisfied	25 (18.0)

RESULTS

Ophthalmic Online Consultation

There were 425 online consultations during the lockdown, with an average of 71 consultations per month, including 14 invalid consultations (3.3%) and 114 repeated consultations (26.8%). The most common reason for consultation was eye discomfort or abnormal appearance (165 visits, 38.8%), and the top three most common manifestations of ocular discomfort were red, swollen, painful eyelids (38, 23.0%); red eyes, itching, blinking or rubbing eyes (27, 16.4%); and red eyes (20, 12.1%) (see **Table 1**).

Socio-Demographic Characteristics

A total of 139 valid questionnaires were collected in this survey from patients who were involved in the online ophthalmic consultation. There were 105 (75.5%) females and 34 (24.5%) males. Those aged between 31 and 40 accounted for a majority of 47 (33.8%). Ethnicity was also recorded, and most patients were Han, 111 (79.9%) with minorities accounting for 28 respondents (20.1%). Most respondents had a bachelor's degree, 91 (65.5%); 40 (28.8%) were health care workers; 100 (71.9%) were staying at home; and 126 (90.6%) had used electronic products, including mobile phones and computers, for a long time. Regarding their sense of trust in and satisfaction with online consultation, 109 (78.4%) trusted the online consultation, 2 (1.4%) distrusted it, and 28 (20.1%) were unsure. More than half said they were satisfied with the online consultation ($n = 82$, 59%), 32 (23%) basically satisfied, and 25 (18%) said they were dissatisfied (see **Table 2**).

Psychological Scale Results and Associated Factors

The median (IQR) scores on the PHQ-9 were 3 (0–6). In all, 52 (37.4%) showed symptoms of depression: mild in 35 (25.2%), moderate in 11 (7.9%), moderately severe in 5 (3.6%) and severe in 1 (0.7%). The median (IQR) GAD-7 scores were 1 (0–4). Thirty-two participants (23.0%) showed symptoms of anxiety and were divided into three groups: mild ($n = 21$, 15.1%), moderate ($n = 5$, 3.6%) and severe ($n = 6$, 4.3%). The median (IQR) ISI scores were 5 (1–9). Symptoms of insomnia were reported in 53 participants (38.1%); 41 (29.5%) reported mild insomnia, 9 (6.5%) reported moderate insomnia symptoms, and 3 (2.2%) reported severe insomnia.

Depression was found to be significantly more common in health care workers ($P = 0.019$). It was also related to their satisfaction with online consultation ($P = 0.024$). There was a tendency in those who had used electronic devices for a long time to suffer from depression ($P = 0.085$). Anxiety was also more common among participants who had used electronics for a long time ($P = 0.038$). There was no significant sociodemographic difference

TABLE 3 | Socio-demographic differences between those with symptoms of depression, anxiety or Insomnia vs. those without depression, anxiety or insomnia.

Variables	Depression[a] Participants, No. (%)			Anxiety[b] Participants, No. (%)			Insomnia[c] Participants, No. (%)		
	Yes	No	*P*[d]	Yes	No	*P*	Yes	No	*P*
Overall	52 (37.4)	87 (62.6)		32 (23.0)	107 (77.0)		53 (38.1)	86 (61.9)	
Gender									
Male	10 (29.4)	24 (70.6)	0.267	8 (23.5)	26 (76.5)	0.935	10 (29.4)	24 (70.6)	0.229
Female	42 (40.0)	63 (60.0)		24 (22.9)	81 (77.1)		43 (41.0)	62 (59.0)	
Ethnic group									
Han	41 (36.9)	70 (63.1)	0.818	23 (20.7)	88 (79.3)	0.199	45 (40.5)	66 (59.5)	0.244
Minorities	11 (39.3)	17 (60.7)		9 (32.1)	19 (67.9)		8 (28.6)	20 (71.4)	
Are you a healthcare worker?									
Yes	21 (52.5)	19 (47.5)	**0.019**	12 (30.0)	28 (70.0)	0.214	17 (42.5)	23 (57.5)	0.5
No	31 (31.3)	68 (68.7)		20 (20.2)	79 (79.8)		36 (36.4)	63 (63.6)	
Current status									
Staying at home	34 (34.0)	66 (66.0)	0.183	24 (24.0)	76 (76.0)	0.661	36 (36.0)	64 (64.0)	0.408
Working outside	18 (46.2)	21 (53.8)		8 (20.5)	31 (79.5)		17 (43.6)	22 (56.4)	
Do you use electronics for a long time?									
Yes	50 (39.7)	76 (60.3)	0.085	32 (25.4)	94 (74.6)	**0.038**	50 (39.7)	76 (60.3)	0.241
No	2 (15.4)	11 (84.6)		0 (0.0)	13 (100.0)		3 (23.1)	10 (76.9)	
Age									
<18	0 (0.0)	5 (100.0)	0.375	0 (0.0)	5 (100.0)	0.738	1 (20.0)	4 (80.0)	0.85
18–25	8 (29.6)	19 (70.4)		5 (18.5)	22 (81.5)		9 (33.3)	18 (66.7)	
26–30	13 (48.1)	14 (51.9)		6 (22.2)	21 (77.8)		12 (44.4)	15 (55.6)	
31–40	18 (38.3)	29 (61.7)		13 (27.7)	34 (72.3)		17 (36.2)	30 (63.8)	
41–50	10 (41.7)	14 (58.3)		7 (29.2)	17 (70.8)		10 (41.7)	14 (58.3)	
51–60	2 (40.0)	3 (60.0)		0 (0.0)	5 (100.0)		3 (60.0)	2 (40.0)	
>60	1 (25.0)	3 (75.0)		1 (25.0)	3 (75.0)		1 (25.0)	3 (75.0)	
Level of education									
Elementary School	1 (14.3)	6 (85.7)	0.231	1 (14.3)	6 (85.7)	0.694	2 (28.6)	5 (71.4)	0.231
Junior High School	1 (16.7)	5 (83.3)		1 (16.7)	5 (83.3)		0 (0.0)	6 (100.0)	
Senior High School	4 (20.0)	16 (80.0)		2 (10.0)	18 (90.0)		5 (25.0)	15 (75.0)	
Bachelor	40 (44.0)	51 (56.0)		24 (26.4)	67 (73.6)		40 (44.0)	51 (56.0)	
Master	4 (40.0)	6 (60.0)		3 (30.0)	7 (70.0)		4 (40.0)	6 (60.0)	
Doctor	2 (40.0)	3 (60.0)		1 (20.0)	4 (80.0)		2 (40.0)	3 (60.0)	
Sense of trust in online consultation									
Trust	38 (34.9)	71 (65.1)	0.139	24 (22.0)	85 (78.0)	0.08	39 (35.8)	70 (64.2)	0.474
Distrust	2 (100)	0 (0.0)		2 (100.0)	0 (0.0)		1 (50.0)	1 (50.0)	
Unsure	12 (42.9)	16 (57.1)		6 (21.4)	22 (78.6)	13 (46.4)	15 (53.6)		
Satisfaction toward online consultation									
Satisfied	24 (29.3)	58 (70.7)	**0.024**	14 (17.1)	68 (82.9)	0.133	27 (32.9)	55 (67.1)	0.237
Basically satisfied	18 (56.3)	14 (43.8)		11 (34.4)	21 (65.6)		16 (50.0)	16 (50.0)	
Dissatisfied	10 (40.0)	15 (60.0)		7 (28.0)	18 (72.0)		10 (40.0)	15 (60.0)	

[a] *Depression was defined as Patient Health Questionnaire-9 score of 5 or higher.*
[b] *Anxiety was defined as Generalized Anxiety Disorder-7 score of 5 or higher.*
[c] *Insomnia was defined as Insomnia Severity Index score of 8 or higher.*
[d] *Chi-square and Fisher's exact tests as appropriate were used to compare the prevalence of mental health symptoms in different populations.*

between those with insomnia vs. those without insomnia (see **Table 3**).

Furthermore, the results of binary logistic regression analysis demonstrated that health care workers were at risk for depressive symptoms (OR: 2.424; 95% CI: 1.143–5.143; $P = 0.021$) (see **Table 4**).

DISCUSSION

This survey revealed the overall prevalence of depression, anxiety, and insomnia symptom was 37.4, 23.0, and 38.1%, respectively. Additionally, depression was found to be significantly more common in health care workers ($P =$

TABLE 4 | Binary logistic regression analysis of risk factors associated with symptoms of depression, anxiety and insomnia.

Variables	Depression[a]			Anxiety[b]			Insomnia[c]		
	OR	95%CI	*P*-value	OR	95%CI	*P*-value	OR	95%CI	*P*-value
Gender									
Male	0.624	0.267–1.458	0.276	1.219	0.47–3.161	0.684	0.604	0.258–1.412	0.244
Female	1[Reference]			1[Reference]			1[Reference]		
Are you a healthcare worker?									
Yes	2.424	1.143–5.143	**0.021**	2.15	0.806–5.732	0.126	1.045	0.443–2.463	0.92
No	1[Reference]			1[Reference]			1[Reference]		
Current status									
Staying at home	0.619	0.287–1.334	0.221	1.933	0.678–5.51	0.217	0.751	0.318–1.777	0.515
Working outside	1[Reference]			1[Reference]			1[Reference]		
Do you use electronics for a long time?									
Yes	3.277	0.691–15.54	0.135	544,474,979.2	0	0.999	2.025	0.525–7.815	0.306
No	1[Reference]			1[Reference]			1[Reference]		

OR, Odds ratio; CI, Confidence interval.

[a]*Depression was defined as Patient Health Questionnaire-9 score of 5 or higher.*

[b]*Anxiety was defined as Generalized Anxiety Disorder-7 score of 5 or higher.*

[c]*Insomnia was defined as Insomnia Severity Index score of 8 or higher. The bold value indicates that the results are statistically significant.*

0.019) and those who were basically satisfied with online consultation ($P = 0.024$). Anxiety was more common among participants who had used electronics for a long time ($P = 0.038$). Interestingly, the current study found health care work was a risk factor for depressive symptoms (odds ratio [OR]: 2.424; 95% CI: 1.143–5.143; $P = 0.021$) among patients who were involved in online consultation for ocular manifestations in the prevailing circumstances of the COVID-19 pandemic.

Under COVID-2019 lockdown circumstances, online consultation became an effective means of responding to the medical needs of non-COVID-19 patients. There were 425 online consultations during the lockdown period from February to August, with an average of 71 visits per month. The number of online consultations was relatively small, and repeated consultations (26.8%) accounted for a high proportion. Many patients consulted for the same problem several times on the same day or the next day, and some even switched doctors to discuss the same problem, mostly symptom complaints. This phenomenon can be explained by patients' desire for an immediate response and their suspicion of online consultations. Meanwhile, we speculated this behavior may be influenced by COVID-19 or it may be due to personality traits. With respect to the cascade of psychological and behavioral effects triggered by the COVID pandemic, it has been shown that the negativity of the psychological effects of the lockdown was further modulated by personality traits, alexithymia, and resilience (14) and that these effects were also correlated with behavioral wellbeing such as emotional eating (15).

According to our survey, 1.4% of the study participants distrusted online consultation; 20.1% were unsure; and 18% were dissatisfied. The COVID-19 pandemic has had an impact on their access to medical care, forcing even those who do not trust in online advice to passively choose online counseling, which may increase their concern about their health. Therefore, online counseling may affect some people's mental disorders and more effort should be made to improve the quality of online medical services. Reasons for online ophthalmology consultations were as follows: 16.4% of 165 visits were for red eyes, itchiness, blinking, or rubbing eyes; 9.1% for dryness; 9.1% for pain; and 2.4% for foreign body sensation. Interestingly, dry eye disease (symptoms including dryness, discomfort, foreign body sensation, pain, itchiness, and so on) can be associated with psychological disorders (16).

In the present study, the prevalence of depression symptom was 37.4% and the insomnia symptom was 38.1%, which were higher than that reported in previous studies. In 2020, a study that surveyed the psychological impact of the pandemic on the general public during the initial stages reported that the prevalence of depression and anxiety symptoms were 30.3 and 36.4%, respectively (17). Remarkably, the prevalence of anxiety symptom reported in this study was 23%, which was lower than reported in previous studies. A meta-analysis during the COVID-19 outbreak showed that the overall prevalence of anxiety was 33%, and a total of 41 studies measured depression and anxiety as indicators of psychological effects. Among these studies, several involved patient populations, which showed that patients with pre-existing conditions or infected by COVID-19 had a higher prevalence of depression and anxiety than health care workers and the general public (18). Our study included people presenting with ophthalmic symptoms, not infected by COVID-19, and the results showed that participants had higher rates of depression and insomnia and lower rates of anxiety than those found in the general population. One important factor that should not be overlooked is that some of the subjects in the current study had dual identities: both health care workers and online consulting patients. Moreover, patients receiving ophthalmic consultation online in the current study were prone to depressive symptoms if they were also health care workers (odds ratio [OR]: 2.424; 95%

CI: 1.143–5.143; $P = 0.021$). Another factor to consider is that the limited sample size may have contributed to the results.

Females were reported to have a higher prevalence of depressive and insomnia symptoms than males, but there was no statistically significant difference observed between females and males in psychological distress across all scales (see **Table 3**). Overall, most studies have revealed that females are more prone to developing mental health symptoms (17–19). In the current study, age was not shown to be associated with psychological distress, which was in accordance with previous studies (20).

In the current study, depression was observed to be significantly more common in health care workers and was also identified as a risk factor for worse depressive symptoms. Additionally, depression was significantly higher in those who were basically satisfied with online consultation. Anxiety and insomnia were also reported more among health care workers, but there was no statistically significant difference between health care workers and non-healthcare workers. As a result of the pandemic, health care workers in different specialties have suffered tremendous psychological pressure, as they not only worried about being infected but also about carrying the virus and infecting their families or colleagues, which may lead to various psychological problems (21–23). Moreover, a heavy workload, wearing protective equipment such as masks and isolation suits for long hours at work, and being in a closed environment for an extended period of time without the ability to drink, eat or use the bathroom for extended periods may aggravate the negative psychological impact on health care providers. In addition, a case of COVID-19 with keratoconjunctivitis as the main symptom has been reported (24), which may increase the number of health care workers in the present study who had eye discomfort or other eye disease psychological burdens. In contrast, a prior study in Singapore suggested that nonmedical health care workers had a higher prevalence of psychological distress because of reduced formal psychological support, less first-hand information, and less training in infection control measures (25).

In the present study, participants who used electronic products for a long time reported more depression, anxiety, and insomnia symptoms than those who did not, and it was significantly associated with anxiety. As a result of the lockdown during the COVID-19 pandemic, people were likely to spend more time on electronic devices, especially young people, exercise less and remain sedentary more, which is detrimental to psychological health (26). Moreover, too much screen time also has an impact on physical health, such as visual fatigue and dry eye. A great number of studies in children and adolescents have shown that high screen time is associated with increased risk of psychological problems (27–29). Additionally, giving more attention to media coverage of the COVID-19 outbreak is associated with higher psychological distress (30). However, in our study, the majority of participants had used electronic products for a long time, but the time giving attention to COVID-19 was unknown. Regarding all these findings, it is necessary to limit screen time and promote physical activities for the mental health of young people.

Specifically, previous publications have shown that decreased vision is known to worsen mental health of eye disease patients (31–33). Among online patients, the number of return visits accounted for 21.4%, including blindness-causing eye diseases such as glaucoma and uveitis that require long-term follow-up treatment. Individuals with glaucoma are more likely to have some or severe anxiety/depression problems than those without glaucoma (34). Therefore, one possible contributing factor of psychological disorders could be vision issues and return visits for consultations about blindness-causing eye diseases.

The results of this study suggest that it is necessary to pay attention to people's mental health and sleep condition in time when public health emergency occurs. The academy of Ophthalmology could team up with the academy of Psychology to come up with strategies to support those at high risk. In the context of COVID-19, online consultation can be regarded as an effective way to solve the medical needs of some people, but it does not significantly alleviate their psychological disorders. There is a need to provide appropriate psychological support for patients who consult online, especially if they were medical staff or had high screen time.

This study has several limitations as follows. First, the sample size of the questionnaire survey was relatively small, so the results may be biased. Second, the prevalence of psychological distress was based on respondents' self-reports rather than clinical diagnosis. Third, the online consultation period spanned several months, while the survey was administered over a two-week period. A longitudinal follow-up is needed to explore the possible long-term relationship between psychological symptoms and the disease. Finally, we did not investigate whether the respondents' ocular symptoms improved, and a control group may be lacking to identify the impact of ocular symptoms on patients' psychological status. The respondents were mainly people with high education levels, so the results of this survey were more likely to reflect their psychological state.

CONCLUSION

During the COVID-19 pandemic and lockdown, psychological distress was highly prevalent among ophthalmological patients consulting with their doctors online. When another public health emergency occurs, special attention should be given not only to patients' ocular symptoms but also to their mental health, and appropriate psychological support should be given, especially for those who are medical staff and those who have used electronic products for a long time. This may mean, for example, encouraging patients to participate in more outdoor activities instead of spending too much time on screen and, if necessary, referring them to a psychiatrist.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Zhongshan Ophthalmic Center, Sun Yat-sen University and People's Hospital of Xinjiang Uygur Autonomous Region. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

LD and NG contributed to analyzing the data and drafting the manuscript. JZ designed the questionnaire and collected the data. DT and AA collected and sorted the data. CZ and ML reviewed and revised the manuscript. All authors contributed to and have approved the final manuscript.

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A Predictive Study Between Anxiety and Fear of COVID-19 With Psychological Behavior Response: The Mediation Role of Perceived Stress

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Objective: Despite the abundance of studies linking fear and anxiety to COVID-19, there are limited studies that examine how these elements impact psychological behavioral responses, especially in Iran. The aim of this study was to investigate the relationship between anxiety and fear of COVID-19 with psychological behavior response, whether this relationship is mediated by role of perceived stress among Iranian population during the COVID-19 pandemic.

Methods: A predictive cross-sectional study was used to investigate the relationships between COVID-19 anxiety syndrome, fear of COVID-19 with psychological behavioral responses due to the pandemic, and the mediating role of the COVID-19 perceived stress in these relationships.

Results: The current study revealed that during the COVID-19 pandemic, fear and anxiety of COVID-19 can influence the psychological behavioral responses of individuals; however, this can be explained through perceived stress.

Conclusion : As such, the current study points out that the individuals who perceived high stress due to COVID-19 were more likely to comply with guidelines, which has given new insight into this field. The current study findings are applicable for health policymakers in order to help them in understanding human behavior for developing health promotion programs and also for fostering resilience among the general population.

Keywords: COVID-19, anxiety, perceived stress, psychological behavior response, global pandemic, COVID-19 anxiety syndrome

INTRODUCTION

The outbreak of the COVID-19 virus has led to millions of deaths globally, forcing governments to take crude measures to halt the spread of the virus. The global pandemic and the subsequent public health measures taken in order to contain the virus have created a profound effect on human life, producing alarming surges in mental health problems, and economic issues (1–5). The prevalence of this virus since December 2019 has long surpassed the rates of infection and death tolls of severe acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS), and Ebola, causing immense psychological difficulties to the general population, which are sequelae linked to fear of infection, provoking a secondary mental health crisis (6–10).

On February 19, 2020, Iran reported its first confirmed case in the city of Qom (11), and by August 2021, the virus had infected over 4.1 million people and caused deaths of at least 94,000 Iranians, becoming the highest death toll in the Middle East (12). Due to COVID-19's alarming speed of infection worldwide, WHO declared it as a pandemic in March 2020 (13). National governments, including Iran, enforced unprecedented reforms, such as lockdowns, quarantine, closures of all non-essential business, social distancing, and intensified hygiene practices in attempt to prevent and reduce the spread of COVID-19 (14). By taking these strict measures, a consequence was the exacerbation of negative psychological responses such as anxiety, stress, uncertainty, fear, and other substantial lifestyle changes among its people (15). Studies have shown that healthcare workers (HCWs) (16), alongside adolescents (17), elderly patients (18), and people who were infected by the coronavirus, were the population hardest hit by the COVID-19 pandemic. Consequently, the COVID-19 psychological impact was observed to be prominent in HCWs (16), students, people with poor health, and women (19, 20) but were lessened when preventive health measures were taken (20), which complied with guidelines and government recommendations (21).

Evidence has shown that high levels of anxiety in Iranians can have negative effects on people's lives and can lead to serious problems (22). Anxiety due to COVID-19 has been associated with contracting and/or dying from COVID-19, fear of their families or loved ones getting infected (23, 24), financial issues (25), and fear of shortage of food, medicine, and other necessities due to panic buying and hoarding (26, 27), thus negatively affecting one's mental health (24). In the same vein, the pandemic has drastically impacted lifestyles, creating anxiety due to social connectedness (28, 29), isolation (30, 31), loneliness (32), and financial hardship (30, 33). This uncontrollable anxiety can lead to an emotional state that may overwhelm the behavior, feelings, and thoughts of the individuals, causing further mental or psychological disorders (34). In addition, obsessive thinking, and other forms of perseveration about COVID-19, may escalate the emergence of clinical anxiety and maladaptive coping (3, 35). Studies have also highlighted that the post-pandemic anxiety may be higher due to the difficulty of returning to "normal" societal functioning, which unavoidably requires exposure to environments related with a greater risk of infection, such as public transport, offices, cinemas, and theaters (35).

During the COVID-19 pandemic, fear has been the most vital and common sentiment with substantial psychological effect on individuals, imploring them to sustain sanitation during the lockdowns and quarantines, thus experiencing stress, anxiety, worry, panic, and phobia to some extent, if it is not well-calibrated (36, 37). Fear can be ascribed to the individual's knowledge of the facts related to that virus either from the media or government bodies, or by directly experiencing the illness or exposure to the indirect experience of a disease outbreak (8, 38–42). Schimmenti et al. (43) categorized fear as: fear for the body, fear for significant others, fear of not knowing, and fear of inaction and past studies have linked fear positively with increased anxiety and depressive symptoms (43–45). Parlapani et al. (19) identified women to have substantially higher levels of fear toward COVID-19 as compared to men, leading participants to have severe depressive and anxiety symptoms. In addition, they discovered that people <30 years old showed less fear of the pandemic. However, severe COVID-19 fear is linked with higher suicide risk (46, 47), psychological distress (5, 48), anxiety and depression (Ahorsu, Lin, Imani, Saffari, Griffiths, (49, 50)), xenophobia and discrimination (51, 52), and pre-existing mental health disorders (53). On the other hand, insufficient fear of the pandemic, whereby the government restrictive measures and policies to combat the pandemic are ignored (45, 54) and COVID-19 vaccine hesitancy (55), may harm the individual and society negatively.

The increasing numbers of COVID-19 infections and mortality have escalated stress (37), which is the main risk factors of mental health problems such as insomnia, anxiety, and depression (49, 54, 56, 57). Stress caused by the pandemic was found to be higher in women (9, 37, 42), younger people (58), those with poor sleeping habits (37, 58, 59), support caregivers, and other minority and disadvantaged groups (60) as they have lower compliance with prevention behavior and/or have less adaptive coping strategies, leading to substantial long-term mental health problems (61). Interestingly, people with higher education were found to have higher level of stress, anxiety, and depression during this pandemic (62), which may be due to their high self-awareness about their health (50).

Despite the abundance of studies linking fear and anxiety to COVID-19, there are limited studies, to the authors' knowledge, that examine how these elements impact psychological behavioral responses, especially in Iran. Hence, this current study was conducted to assess two research objectives, the first is to determine the effect of COVID-19 anxiety syndrome and fear of COVID-19 on psychological behavioral responses in Iran. The second objective evaluated the role of stress in mediating the relationships between COVID-19 anxiety syndrome and fear of COVID-19 on psychological behavioral responses among the Iranian people. The psychological and behavioral responses of COVID-19 in Iran is crucial to enhance resilience and to decrease the population's vulnerability.

TABLE 1 | Demographic characteristics of participants ($n = 926$).

Variables	*n* (%)
Gender	
Female	782 (85.2)
Male	137 (14.8)
Marital status	
Single	286 (30.9)
Married	640 (69.1)
Education level	
Under diploma	19 (2.1)
Diploma	128 (13.8)
Upper Diploma	58 (6.3)
Bachelor	417 (45.0)
Master	243 (26.2)
Ph.D.	54 (5.8)

METHODS

A predictive, cross-sectional online questionnaire-based survey was used in this study to investigate the relationships between COVID-19 anxiety syndrome, fear of COVID-19 with psychological behavioral responses due to the pandemic, and the mediating role of the COVID-19 perceived stress in these relationships.

Participants

The requisite sample size was estimated to be 1,000, with a probability of 0.05, a statistical power of 80%, an anticipated medium effect size of 0.12, and 31 items measuring four constructs. This estimate was calculated *a priori* using a sample size calculator for Structural Equation Models (SEM) (63). The minimum statistical power analysis in humanities and social sciences studies should be 80% (64). In total, 926 participants in Iran participated between October and November 2020 during the initial stages of the COVID-19 pandemic. The online scales were created *via* Google Forms and its URL link was sent by email or social networking applications such as a Telegram channel or WhatsApp group of adults. The inclusion criteria for participants were adults (age $>$ 18) who were willing to participate in this study. The mean age of participants was 31.12 (SD = 7.62) (range 18 to 67) years old, and most were female (85.2%), married (69.1%), and had a bachelor's degree (45.0%). Other socio-demographic information is provided in **Table 1**.

Instruments

A demographic form and the Persian version of the following scales were used in this study.

Perceived Stress Scale

The PSS-10 is a self-reported scale to measure the global level of perceived stress (65). This scale includes two factors: Factor 1 (Perceived Helplessness) is made of negatively phrased items (i.e., items 1, 2, 3, 6, 9, and 10; e.g., "In the last month, how often have you felt nervous and stressed?"), and Factor 2 (Perceived Self-Efficacy) is made of positively phrased items (i.e., items 4, 5, 7, and 8; e.g., "In the last month, how often have you felt that things were going your way?").

The Persian Version of the COVID-19 Anxiety Syndrome

This self-report measure includes nine items, loading on two factors, assessing features of the anxiety syndrome linked to COVID-19. These are (1) avoidance (e.g., of public transport because of the fear of contracting COVID-19); (2) checking (e.g., of symptoms of COVID-19); (3) worrying (e.g., researching symptoms of COVID-19 at the cost of other activities); and (4) threat monitoring (e.g., paying close attention to others displaying possible symptoms of COVID-19. Items relating to checking, worrying, and threat monitoring load on the first factor ("perseveration") with a second factor comprising avoidance items ("avoidance"). Participants are asked to rate how frequently they experience each feature of the anxiety syndrome using a 5-point time anchored scale (0 = "Not at all" to 4 = "Nearly every day over the last 2 weeks"). Scores range between 0 and 36, with higher scores indicative of increased levels of the anxiety syndrome. The C-19ASS has demonstrated good reliability and validity (35). In the current study, the Cronbach α was 0.82.

The Persian Version of the Fear of COVID-19

The FCV-19S (44) is a seven-item scale that assesses the fear of COVID-19. The seven items (e.g., "I am most afraid of coronavirus-19") are rated on a 5-point scale from 1 (strongly disagree) to 5 (strongly agree) with scores ranging from 7 to 35. The higher the score, the greater the fear of COVID-19.

The Persian Version of the Psychological Behavioral Responses

The PBR (66) is a self-reported measure that assesses the characteristics of psychological and behavioral responses in COVID-19. This measure includes 5 items with scores ranging from 1 (never) to 4 (always) and has good validity and reliability.

Data Analysis

To assess factor structure, exploratory factors analysis (EFA) was performed through maximum likelihood with Promax rotation using SPSS version 26. The Kaiser–Meyer–Olkin (KMO) and the Bartlett's test of sphericity were employed to ensure the study sample was appropriate to perform the factor analysis. Items with absolute loading below 0.5 were removed (67). Next, following the two-step approach, this study employed covariance-based structural equation modeling and Amos version 27 to test the measurement model and structural model. First, to assess the measurement model, the maximum likelihood confirmatory factor analysis (CFA) was performed. Model fit was assessed using several model fit indexes and the model was revised according to the modification indices (67). The internal consistency of each construct was assessed using its Cronbach's alpha. Construct reliability was assessed using composite reliability (CR) and maximal reliability (MaxR). The convergent validity

was assessed through average variance extracted (AVE) of the latent constructs. Cronbach's alpha, CR, and MaxR were >0.7, indicating good internal consistency and construct reliability, while AVE of >0.5 indicates good convergent validity. To establish discriminant validity, the heterotrait–monotrait ratio of correlation (HTMT) matrix with values <0.85 was considered acceptable discriminant validity (68). Next, the proposed model and hypothesis were tested. In order to test the hypotheses in the structural model, bootstrapping with 2,000 replications was performed (67). All tests in this study were two-tailed, and p values of <0.05 were considered statistically significant.

Ethical Considerations

The study aims, number of items, time to complete the survey, the researchers' affiliation and email for queries, and the ethical code of study were inserted on the first page of the online questionnaire. These items informed participants that their participation was voluntary and that their responses would be published anonymously as group data. The protocol of this study was approved by the Mazandaran University of Medical Sciences Research Ethics Committee (IR.MAZUMS.REC.1400.13728).

RESULTS

The results of the maximum likelihood EFA with Promax rotation extracted five factors, in which COVID-19 anxiety syndrome was divided into two factors, namely, perseverate thinking (five items) and avoidance (four items). The values of Kaiser–Meyer–Olkin (KMO) was 0.911 and Bartlett's test of sphericity showed the adequacy of the sampling and suitability of the data for performing the factor analysis ($p < 0.001$, $\chi^2 = 10{,}557.720$, df = 300). One item from perceived stress and two items from psychological behavioral responses were removed due to weak factor loadings of <0.5. The final factor structure explained 57.793% of the variance.

The maximum likelihood CFA was performed to assess the measurement model based on the factor structure obtained from EFA. The results showed that the initial measurement model with all first-order construct did not fit the data well [$\chi^2(242) = 1{,}283.852$, $p < 0.001$, $\chi^2/df = 5.305$, CFI = 0.898, IFI = 0.898, TLI = 0.883, SRMR = 0.059, and RMSEA (90% CI) = 0.068 (0.065, 0.072)]. Following the results of modification indices, five pairs of the item measurement error (i.e., anxiety syndrome—two pairs; fear of COVID-19—three pairs) were allowed to freely covary to improve the model fit. The revised measurement model with all first-order constructs has improved significantly [$\Delta\chi^2 (\Delta df = 4) = 411.581$, $p < 0.001$] and fitted the data well [$\chi^2(238) = 872.271$, $p < 0.001$, $\chi^2/df = 3.665$, CFI = 0.938, IFI = 0.938, TLI = 0.928, SRMR = 0.053, and RMSEA (90% CI) = 0.054 (0.050–0.058)]. Next, COVID-19 anxiety syndrome was included in the revised measurement model as second-order construct, and the results showed that the final measurement model fit also fitted the data well [$\chi^2(240) = 1{,}016.966$, $p < 0.001$, $\chi^2/df = 4.237$, CFI = 0.924, IFI = 0.924, TLI = 0.912, SRMR = 0.053, and RMSEA (90% CI) = 0.059 (0.055, 0.063)], and all factor loadings were >0.5 and significantly.

Table 2 shows the results of the measurement model assessment. All constructs (both first-order and second-order constructs) showed good internal consistency (Cronbach's alpha ranged from 0.721 to 0.886), and construct reliability (CR ranged from 0.724 to 0.876, MaxR ranged from 0.732 to 0.889). As shown in **Table 2**, all constructs' AVE was >0.5, except for construct of avoidance (0.398) and psychological behavioral responses (0.471). Although the AVE for these two constructs was <0.5, Fornell and Larcker (69) recommended that if AVE is <0.5, CR of >0.7 alone can be used to establish convergent validity of the construct. Indeed, AVE is a strict measure of convergent validity and a more conservative measure than CR (70). Therefore, all constructs have achieved convergent validity.

Table 3 shows the results of HTMT matrix, and all values in the HTMT matrix were <0.9, demonstrating the acceptable discriminant validity of all constructs.

Next, the proposed structural model and hypotheses were tested while controlling for the effect of participants' age, gender, marital status, and education level. The results of the structural model assessment are shown in **Table 4**. The results of assessing total effect showed a significant positive relationship between COVID-19 anxiety syndrome and psychological behavioral responses ($b = 0.767$, $p < 0.001$), and between fear of COVID-19 and psychological behavioral responses ($b = 0.121$, $p < 0.001$), providing support for H1 and H2. The total effect model explained 68% of the total variance of psychological behavioral responses. Moreover, the results of assessing direct effect showed a significant positive relationship between COVID-19 anxiety syndrome and perceived stress ($b = 0.113$, $p < 0.01$), between fear of COVID-19 and perceived stress ($b = 0.455$, $p < 0.001$), and between perceived stress and psychological behavioral responses ($b = 0.100$, $p < 0.001$); thus, H3, H4, and H5 were supported. Lastly, using a bootstrapping approach, the results of assessing indirect effects supported H6 and H7 on the positive mediation role of perceived stress in the relationship between COVID-19 anxiety syndrome and psychological behavioral responses ($b = 0.011$, $p < 0.01$) and between fear of COVID-19 and psychological behavioral responses ($b = 0.046$, $p < 0.001$). The significant direct relationship between COVID-19 anxiety syndrome and psychological behavioral responses ($b = 0.756$, $p < 0.001$) and between fear of COVID-19 and psychological behavioral responses ($b = 0.075$, $p < 0.01$) indicates that the mediation role of perceived stress for both relationships was partial.

The mediation model explained 70% of the total variance of psychological behavioral responses and 33% of the total variance of perceived stress. **Figure 1** shows the results of the structural model.

DISCUSSION

The current study sought to assess the relationship between COVID-19 anxiety syndrome and fear of COVID-19 with psychological behavioral responses. Moreover, the study aimed to examine whether the COVID-19 perceived

TABLE 2 | Results of the Measurement model assessment.

Construct	Factor loading	Cronbach's alpha	CR	MaxR	AVE
First order construct					
Perseverate thinking					
Item 1	0.659	0.846	0.844	0.860	0.524
Item 2	0.588				
Item 3	0.814				
Item 4	0.825				
Item 5	0.706				
Avoidance					
Item 1	0.538	0.721	0.724	0.732	0.398
Item 2	0.684				
Item 3	0.671				
Item 4	0.618				
Fear of COVID-19					
Item 1	0.758	0.886	0.876	0.889	0.506
Item 2	0.813				
Item 3	0.611				
Item 4	0.740				
Item 5	0.793				
Item 6	0.538				
Item 7	0.678				
Perceived Stress					
Item 1	0.722	0.863	0.863	0.868	0.559
Item 2	0.789				
Item 3	0.792				
Item 5	0.683				
Item 6	0.746				
Psychological Behavioral Responses					
Item 3	0.546	0.721	0.724	0.755	0.471
Item 4	0.798				
Item 5	0.691				
Second order construct					
COVID-19 Anxiety Syndrome		0.830	0.749	0.895	0.559
Perseverate thinking	0.578				
Avoidance	0.943				

TABLE 3 | Discriminant validity assessment using HTMT matrix.

		(1)	(2)	(3)	(4)	(5)
Heterotrait-monotrait ratio of correlations (HTMT)	**First order construct**					
	Perseverate thinking					
	Avoidance	0.552				
	Fear of COVID-19	0.615	0.482			
	Perceived Stress	0.343	0.237	0.505		
	Psychological Behavioral Responses	0.252	0.834	0.306	0.065	
	Second order construct					
	(6) COVID-19 Anxiety Syndrome			0.645	0.344	0.564

stress mediates the relationship between COVID-19 anxiety syndrome, fear of COVID-19, and psychological behavioral responses.

The findings revealed that there was a significant positive correlation between COVID-19 anxiety syndrome and psychological behavioral responses. This finding aligns with

TABLE 4 | Structural model assessment.

Paths	Unstandardized Path coefficients	95% confidence level (Lower Bound, Upper Bound)
Total Effect		
COVID-19 Anxiety Syndrome → Psychological Behavioral Responses	0.767***	(0.708,0.832)
Fear of COVID-19 → Psychological Behavioral Responses	0.121***	(0.089,0.155)
Direct Effects		
COVID-19 Anxiety Syndrome → Perceived Stress	0.113**	(0.043,0.188)
Fear of COVID-19→ Perceived Stress	0.455***	(0.412,0.496)
Perceived Stress → Psychological Behavioral Responses	0.100***	(0.074,0.127)
COVID-19 Anxiety Syndrome → Psychological Behavioral Responses	0.756***	(0.698,0.820)
Fear of COVID-19→ Psychological Behavioral Responses	0.075**	(0.041,0.112)
Mediation Effects		
COVID-19 Anxiety Syndrome → Perceived Stress → Psychological Behavioral Responses	0.011**	(0.004,0.021)
Fear of COVID-19 → Perceived Stress → Psychological Behavioral Responses	0.046***	(0.033,0.060)

*** $p < 0.001$, ** $p < 0.05$; *Control variables: age, gender, marital status, and education level.*

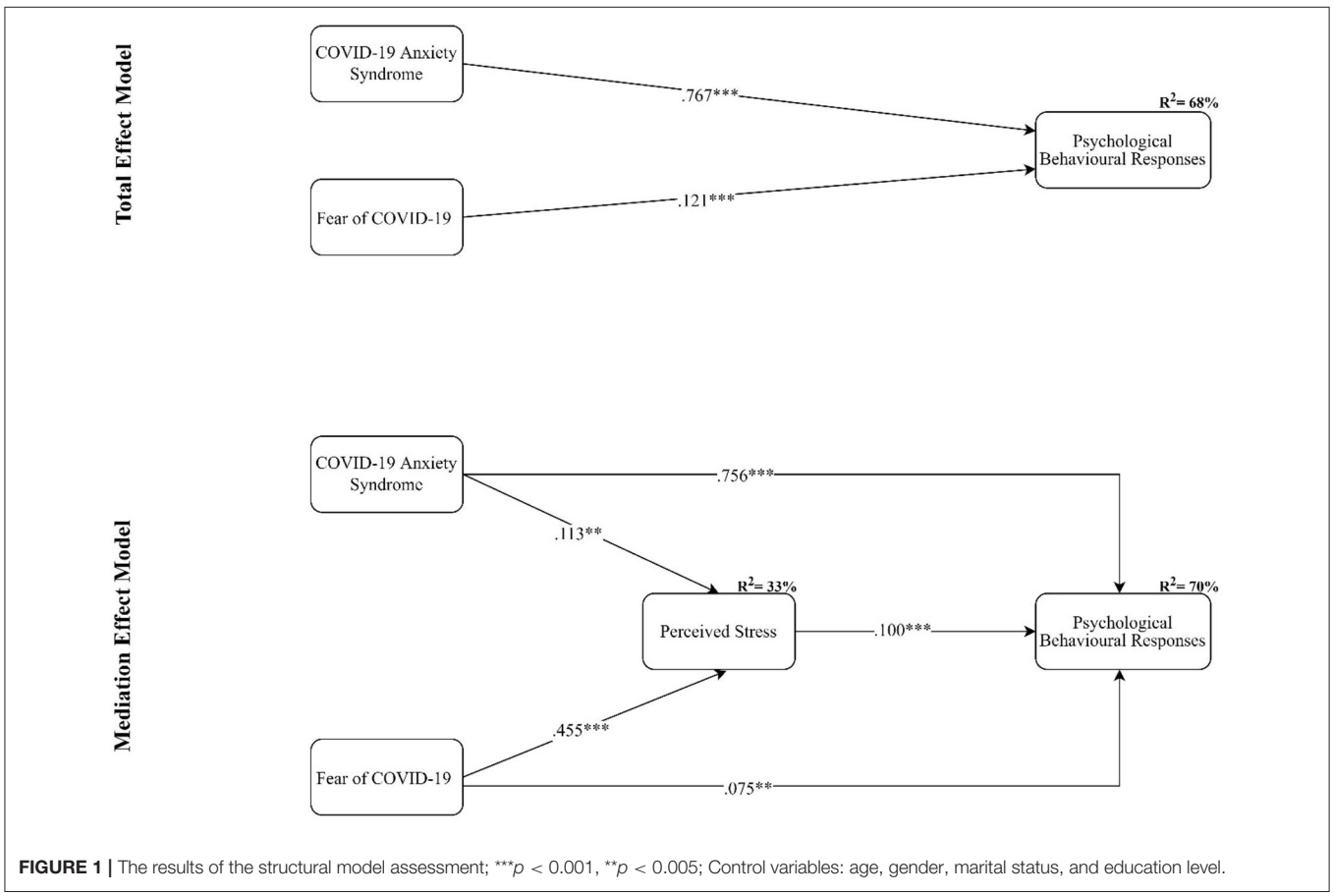

FIGURE 1 | The results of the structural model assessment; ***$p < 0.001$, **$p < 0.005$; Control variables: age, gender, marital status, and education level.

previous studies in determining a positive relationship between the COVID-19 anxiety syndrome and psychological behavioral responses such as depression, feelings of helplessness, persistent worrying, and never feeling clean after disinfecting (71). Pandemic psychological distress can shape the behavior (35) and it has been identified that people usually experience fear, sense of isolation (72), and a wide range of behavioral change (73) during novel pandemics (74). However, in response to the stress experienced by people as a result of COVID-19, there are many behavioral changes that have led to over-compliance with health protocols as well as many reports of non-compliance with these protocols such as wearing masks and hand washing (39). The current article has identified that a person's gender, age, and educational level have increased the

likelihood of non-compliance with COVID-19-related public health measures. The findings of a longitudinal cohort study have indicated that non-compliance, especially with hygiene-related measures, was more prevalent in male participants and individuals with higher educations (75). This is why we have controlled the effects of gender, age, and education during the data analysis.

The current study also explored the positive correlation between fear of COVID-19 and psychological behavioral responses. According to the protection motivation theory (PMT), which proposed key contributors to people's willingness to make behavioral changes (76), the extent of the fear that the individual perceives, as well as the other factors such as coping skills, have the potential to determine individuals' behavioral response. The COVID-19 pandemic formed several fears for people such as fear of being contaminated (72) or the fear of the unknown (77, 78) that can trigger elements related to psychological behavioral responses. Due to the novel nature of the current pandemic with a rapid person-to-person transmission, as well as its potential for transmission from asymptomatic carriers, individuals may experience a threat that causes fear (19, 79). Fear of COVID-19 can lead to protective behaviors (49). It has been revealed by research (54) that fear of COVID-19 was the only predictor of positive behavior change such as improved hand hygiene or social distancing. Interestingly, they found that the COVID-19 fear and anxiety were stronger predictors than moral and political orientation (54). Similarly, fear can significantly increase individual engagement in preventive behaviors during the COVID-19 pandemic (80). It is worth mentioning that the relationship between fear and health behaviors is 2-fold. A study conducted in Greece (2020) among 3,029 participants indicated that the greater application of safety or checking behaviors, as well as a high level of compliance with guidelines, led to an amplification of fear, potentially due to increased contamination awareness (19).

It has been suggested by the current study that there is a significant positive relationship between COVID-19 anxiety syndrome and perceived stress. Also, the significant positive correlation between fear of COVID-19 and perceived stress was shown by the current study's findings. The person's appraisal of a stressor as threatening or not, as well as her/his own abilities to cope can indicate the perceived stress level (81). Several factors such as the inconsistency between policies and scientific evidence (82), the lockdown policies and quarantine (83, 84), evidences of possible fatal consequences of contracting the virus (85), repeated exposure to media reports (52), and the individual psychological trait (86) influence the perceived stress associated with COVID-19. The findings of an Iranian study have indicated that the most stressful event during the COVID-19 outbreak was the rise in essential goods prices. They have also found that the death of a family member due to COVID-19 infection was the main source of perceived stress (87). The anxiety and fear of contracting COVID-19 are also identified as the most important underlying factor influencing the level of COVID-19 perceived stress. The findings of a study (88) showed that higher COVID-19 perceived stress was associated with more emotional distress including fear and anxiety. It has been indicated that perceived stress due to COVID-19 among the Iranian general population was slightly high, and it has been correlated with using social media (89). Previous studies have also shown that, in some cases, social media can increase the perceived risk of the outbreaks (90). The findings of a large national study in Iran found a high level of stress among the general Iranian population during the COVID-19 outbreak in which those in middle age groups and low to moderate socioeconomic status experienced the highest stress due to worry about losing their jobs or income (91).

The findings of the current study showed that there is a positive significant correlation between the perceived stress of COVID-19 and psychological behavioral responses. Furthermore, the perceived stress of COVID-19 mediated the relationship between COVID-19 anxiety and fear of COVID-19, and psychological behavioral responses. Although there are studies that indicate that the more the individual perceives the stress, the higher the potential for engaging in unhealthy behaviors (92), the current study showed a contradictory finding. As such, the current study points out that the individuals who perceived high stress due to COVID-19 were more likely to comply with guidelines. This finding is supported by previous findings that indicated that practicing precautionary behaviors during the COVID-19 pandemic is strongly associated with perceived stress (66, 93). Some existing studies addressed the mediating role of perceived stress in relationships between different concepts and psychological behavioral responses in different settings. For example, a study conducted by Pfeffer et al. (94) indicated the moderating role of perceived stress and trait self-control in the context of intention and physical activity behavior. It has also been found that nearly half of the total effect of self-compassion on health behavior occurred through perceived stress (95). According to the transactional stress model (96), individuals' reactions and adaptation to the objective stressful events are determined by their cognitive appraisal of the stressors such as perceived stress. It has been addressed by the studies' findings that those individuals who perceive the high levels of stress may have more difficulty in realizing positive cognition, emotion, and behaviors and are at a greater risk for health problems (88, 97). However, the current study indicated that the more individuals perceived the COVID-19 stress, the higher the compliance with the protective measures. In line with this finding, a cross-sectional study with 3,727 Iranian participants revealed that respondents were motivated by the COVID-19 danger and fear control responses that indicates their high perceived efficacy (98). The extended parallel process model (EPPM) (99) suggests supporting theoretical explanation for the current study finding. EPPM suggests that individuals who are exposed to a risky situation usually apply two types of cognitive appraisal, namely, the efficacy of the recommended advice and perceived threat. Accordingly, individuals who perceive the COVID-19 threat in high levels while perceiving low efficacy usually act to protect themselves from the fear rather than the danger itself (fear control process). Instead, those who perceive high efficacy, even if they perceive a high level of threat, usually will be motivated to protect themselves from the danger (danger control process).

Study Limitations

While the study provides new information relative to the mediating role of the perceived stress on the relationship between COVID-19 anxiety syndrome, fear of COVID-19, and psychological behavioral responses, it is not without its limitations. The cross-sectional design of this study does not allow for firm causal conclusions. Conducting longitudinal studies by collecting data at different points in time as well as experimental studies are recommended for future research since there are numerous complex and dynamic processes by which spirituality relates to mental health outcomes. In terms of mediation studies, the most salient mediating processes seem to involve stress dimensions, values/attitudes, and social control/norms, which need to be investigated in further studies. Furthermore, the data were gathered *via* online data collection. Despite its advantages (e.g., affordability and accessibility), online surveys have been criticized for selection bias and difficulty reaching certain types of participants (100, 101).

CONCLUSION

The current study revealed that during the COVID-19 pandemic, fear and anxiety of COVID-19 can influence the psychological behavioral responses of the individuals; however, this can be explained through perceived stress. The visibility of protective factors in addition to risk factors can offer a broader view on measures to deal with depression in the general population resulting from global adverse situations such as the ongoing COVID-19 pandemic. The current study findings are applicable for health policymakers to help them in developing health promotion programs and fostering resilience among the general population. Also, it is useful for organizations and workplaces because they have been known as the best place to provide psychological support to the general population. Workplaces have a considerable role in preventing the spread of COVID-19 infection, and conducting health promotion programs to increase psychological skills and coping mechanisms to address the negative effects of the COVID-19 pandemic (102).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Mazandaran University of Medical Sciences Research Ethics Committee (IR.MAZUMS.REC.1400.13728). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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BRIEF RESEARCH REPORT
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Validation of the Peruvian Spanish Version of the Stress and Anxiety to Viral Epidemics-6 Scale to Measure Viral Anxiety of Medical Students During COVID-19

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Introduction: The COVID-19 pandemic has created academic problems for Peruvian medical students leading to anxiety and depression. Hence, validated scales, such as the Stress and Anxiety to Viral Epidemics-6 items (SAVE-6), are required to identify and propose interventions to improve mental health. We aimed to perform a psychometric validation of the Peruvian version of SAVE-6 on medical students during the COVID-19 pandemic in Lima, Peru, in 2022.

Methods: A total of 260 medical students at National University of San Marcos (UNMSM) participated in an online survey in January 2022. We collected sociodemographic characteristics and classified psychiatric symptoms using SAVE-6, the Generalized Anxiety Disorder-7 items (GAD-7) scale, and the Patient Health Questionnaire-9 items (PHQ-9). We performed confirmatory and parallel factor analysis to examine the validity of the Peruvian Spanish version of SAVE-6.

Results: We explored the reliability and validity of SAVE-6 and SAVE-6 after excluding item 5, since factor loading of item 5 is too low. Both scales showed good internal consistencies (Cronbach's $\alpha = 0.780$ and.82 and McDonald's $\Omega = 0.792$ and.829, respectively). Furthermore, SAVE-6 after excluding item 5 showed good convergent validity with GAD-7 ($r = 0.224$, $p < .001$) and PHQ-9 ($r = 0.217$, $p < .001$). Consequently, instead of the full SAVE-6, SAVE-6 excluding item 5 proved to be reliable and valid enough to assess the anxiety of Peruvian medical students during the pandemic.

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Conclusion: The Peruvian Spanish SAVE-6 scale excluding item 5, rather than the full SAVE-6, can be applied to measure viral anxiety of medical students in Peru with good validity and reliability.

Keywords: medical students, COVID-19, SAVE-6, anxiety, stress, Peru

INTRODUCTION

The COVID-19 pandemic has had a considerable impact worldwide. As the World Health Organization (WHO) stated, deaths due to COVID-19 have exceeded five million, of which more than two million have been in the Americas (1). According to the data reviewed on March 15th 2022, ∼200,000 deaths have been reported in Peru[1], making it the country with the highest mortality rate (650.80 deaths per 100,000 inhabitants) and the third highest fatality rate (6.9%) in the world (2).

As part of the contingency plan for the pandemic, Peruvian universities established physical distancing measures that included only online classes, which meant no hospital rotations for medical students. This has been a mental challenge for students and may have frustrated their personal expectations. A systematic review and meta-analysis reported an increased prevalence of depression (39%) and anxiety (36%) in university students during the pandemic (3). Specifically, in medical students in China, the presence of COVID-19-related psychological distress was evident in ∼27% of participants and 11% showed an acute stress reaction (4). Another study involving Chinese medical students during the initial phase of the pandemic reported that 0.9% of students showed severe anxiety symptoms, 2.7% had moderate symptoms, and 21.3% had mild symptoms (5). In Peru, an observational study on university students from different regions found that 51.2% of them showed medium-to-moderate levels of anxiety and 45% showed medium-to-high levels of depression (6). Additionally, a study conducted on first-year medical students in Lima, Peru revealed that 75.4% of participants manifested some degree of anxiety during COVID-19 (7).

Evidence suggests that the COVID-19 pandemic has a negative global impact on the mental health of students. College students often face stressful events such as a difficult study program, difficult assignments and projects, financial problems, and uncertainty about their future, and such challenges must be faced emotionally. This translates into higher rates of stress and anxiety compared to those in the general population (8). Evidently, during the pandemic period, mental health problems, such as anxiety (9), depression (10), and post-traumatic stress disorder (11), have increased. In a study by Son et al. (12) on university students, 71% of the participants had increased stress and anxiety levels owing to the COVID-19 pandemic. Additionally, studies show that the prevalence of depression, anxiety, and/or suicidal thoughts has assumed alarming proportions among college students (13). In turn, studies indicate that medical students are particularly vulnerable to poor mental well-being and psychological distress compared to the general population. In a research conducted by Saddik et al. (14), anxiety levels and the effects of online education on anxiety levels differed between medical students and the general university population.

Medical students must maintain optimal mental health through specific measures to ensure the continuity of their education and their subsequent successful professional practice, which involves promotion, prevention, and intervention in people's health (15, 16). Medical schooling is inherently a challenging and stressful academic experience that can make medical students vulnerable to depression, anxiety, and burnout. Studies investigating the mental health of practicing physicians have shown that stress that begins in medical school tends to continue throughout the years of medical practice (15). After medical school, a physician also often lends himself to a chronically stressful lifestyle (16). Owing to the COVID-19 pandemic, medical students are unprepared for situations of uncertainty in clinical practice, which can generate anxiety and stress and impact mental wellbeing (17). Therefore, simple questionnaires are needed to enable appropriate screening of these problems, as timely detection of anxiety in medical students is critical to proposing specific interventions to maintain their mental health and ensure proper development of their academic activities and future professional work.

There are scales to measure these problems, such as the COVID-19 Anxiety Scale (CAS-7) (18), the Fear of COVID-19 Scale (FCV-19S) (19), the Coronavirus Anxiety Scale (CAS) (20), and the Stress and Anxiety to Viral Epidemics-6 Items (SAVE-6) scale (21). CAS-7 (18) and FCV-19S (19) include items pertaining to worry, increased heartbeat, or repetitive thoughts, and CAS (20) includes items of physiological arousal symptoms associated with clinically elevated fear and anxiety. In our unpublished work on comparing these scales in the general population (22), CAS was the most discriminating and difficult, SAVE-6 was the least discriminating, and CAS-7 and FCV-19S were moderately discriminating. In this study, we attempted to screen medical students who needed psychological support for their anxiety regarding the pandemic in clinical clerkship rather than screening them for mental health impairments, and we considered that SAVE-6 was appropriate for the study objective.

The SAVE-6 is a self-reported questionnaire, in which each item is graded according to a Likert scale, receiving a value of 0 (never) to 4 (always), with a total score between 0 and 24 (21). It was developed to measure individual levels of anxiety regarding the pandemic among the general population derived from one of two factors (factor I—anxiety about the epidemic) of the SAVE-9 scale, which was developed for assessing work-related stress and anxiety specifically in response to the COVID-19 epidemic (23). SAVE-6 has already been validated in the general populations

[1]https://covid19.minsa.gob.pe/sala_situacional.asp (accessed March 23, 2022).

in South Korea (21), Lebanon (24), Bangladesh (25), and the United States (26). It was also applied with good reliability and validity to special populations, such as public-sector workers (27), cancer patients (28), medical students (29), and healthcare workers (30). In a study conducted on medical students in South Korea (29), where the psychometric properties and convergent validity of SAVE-6 were explored, the single-factor structural model of SAVE-6 was found to have good internal consistency (Cronbach's $\alpha = 0.756$) and good convergent validity with the Generalized Anxiety Disorder-7 items (GAD-7) scale, CAS, and Work and Social Adjustment Scale (WSAS). Moreover, through receiver operating characteristic analysis, the appropriate cutoff score was determined as 15 points in accordance with at least a mild degree of generalized anxiety.

The present study was developed during the so-called third wave that referred to the rapid increase in positive cases of COVID-19 between December 2021 and March 2022[2]. With the vaccination process, which has slowed down[2], and the constant political changes in Public Health (7 Ministers of Health since the first reported case of COVID-19 in Peru), there is no good expectation in the short and medium terms. Since the situation is not favorable in Peru, the necessary preventive measures in Public Health for new outbreaks or different pandemics are not being taken, and obtaining a reliable and valid instrument to measure anxiety due to COVID-19 among medical students in Peru is crucial, the validation of SAVE-6 could be an attractive alternative because standardized health indicators will be available for international comparative studies (31). Therefore, we aimed to perform a psychometric validation of the Peruvian version of SAVE-6 on medical students during the COVID-19 pandemic in Lima, Peru, in 2022.

METHODS

Participants and Procedure

For this psychometric validation study, we calculated a sample of 281 students (with a type 1 error of 5% and an estimated proportion of 50%) for a total finite population of 1,050 medical students enrolled at National University of San Marcos (UNMSM) during the 2021–22 period. We collected data through an online survey in Google Forms in January 2022. During this time, we received results from 260 students, which represents an estimated sample for a type 1 error of 5.3%. The survey was sent through institutional emails provided by the UNMSM medical school. In Peru, medical school is divided into 7 years. In general, the curriculum is divided into pre-medical (first year), pre-clinical (second and third years), clinical (fourth to sixth years), and medical internship (seventh year) where the students gain practical experience in hospitals. In this study, students who provided consent and provided complete information were eligible to participate. The survey form was developed according to the Checklist for Reporting Results of Internet e-Surveys (CHERRIES) guidelines (32), and investigators checked the usability and technical functionality of the survey form before implementation. The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine of UNMSM (application #0165).

[2]https://www.minsa.gob.pe/reunis/data/vacunas-covid19.asp (accessed March 23, 2022).

Sociodemographic Characteristics

We collected the following data: age, sex, and grade (number of years the student is studying at the time of the survey and can vary from 1 to 7 years).

Measures

Stress and Anxiety to Viral Epidemics-6 Items Scale

The SAVE-6 scale is a self-reported rating scale, which was developed for assessing one's pandemic-related anxiety (21). It was derived from the original SAVE-9 scale, which was developed to measure healthcare workers' occupational stress and anxiety response to the COVID-19 epidemic (23). SAVE-9 was clustered around two factors: Factor I—"Anxiety about the epidemic" (items 1, 2, 3, 4, 5, and 8, namely SAVE-6) (21) and Factor II—"Work-related stress associated with the epidemic" (items 6, 7, and 9, namely SAVE-3) (33). In this study, we applied the SAVE-6 scale, which can be applied to the general population, rather than SAVE-9, which was developed for healthcare workers. While medical students can play roles similar to healthcare workers, they do not actually work as healthcare workers. Item 9 of SAVE-9 ("Do you think that your colleagues would have more work to do due to your absence from a possible quarantine and might blame you?") was not appropriate for application to medical students who do not work and are not replaced by other medical students. Additionally, items 6 and 7 can be confusing to medical students (29); hence, we determined SAVE-6 to be more applicable to medical students.

The 6 items of SAVE-6 are rated on a Likert scale ranging from 0 (never) to 4 (always). A higher total score reflects higher levels of anxiety. In this study, we translated the SAVE-6 scale using a translation and back-translation method. The translation team comprised a bilingual Peruvian translator expert in linguistics, who oversaw both the direct and reverse translation process. Together with this expert, the researchers oversaw semantic verification of the Spanish version of the SAVE-6 questionnaire (https://www.save-viralepidemic.net) to adapt it to the Peruvian context. To check the understanding of the adaptation, we conducted a pilot test with 30 medical students who were not included in our last sample.

Generalized Anxiety Disorder-7 Items

The GAD-7 scale is a self-reported scale for measuring the severity of general anxiety (34). The 7 items of GAD-7 are rated on a 4-point Likert scale ranging from 0 (not at all) to 3 (nearly every day). A higher total score means higher levels of general anxiety. The Spanish version of GAD-7 (from Spain) was previously applied in Peru on medical students (7), which was validated in Spain among the general population (35). In this study, we applied the Spanish version of GAD-7 (35), and Cronbach's α in this sample was 0.736.

Patient Health Questionnaire-9 Items

The PHQ-9 is a self-reported rating scale for measuring the severity of depression (36). The 9 items of PHQ-9 are rated on a 4-point Likert scale ranging from 0 (not at all) to 3 (nearly every day). A high total score means severe levels of depression. In this study, we applied the Peruvian Spanish version of PHQ-9 (37) validated among medical students, and Cronbach's α in this sample was 0.883.

Statistical Analysis

We explored the construct validity and reliability of the Peruvian Spanish version of SAVE-6. Normality was checked based on skewness and kurtosis values of each item within the range ± 2 (38). To check the sampling adequacy and data suitability for factor analyses, the Kaiser–Meyer–Olkin (KMO) value and Bartlett's test of sphericity were examined. Confirmatory factor analysis (CFA) with the diagonally weighted least squares method was conducted to check the factor structure of the Peruvian Spanish version of SAVE-6. A satisfactory model fit for the factor structure was defined by a standardized root-mean-square residual (SRMR) value ≤.05, root-mean-square-error of approximation (RMSEA) value ≤.10, and comparative fit index (CFI) and Tucker–Lewis index (TLI) values ≥.90 (39, 40). Multi-group CFA was conducted to examine whether the Peruvian Spanish version of SAVE-6 can measure the pandemic-related anxiety of medical students in the same way between sexes, among those with depression (PHQ-9 ≥ 10), or those with anxiety (GAD-7 ≥ 10). Internal consistency reliability was tested based on Cronbach's α and McDonald's Ω. Convergent validity of the Peruvian Spanish SAVE-6 with pre-existing GAD-7 and PHQ-9 scales were tested by Pearson's correlation coefficients. Psychometric properties were also assessed by conducting the item response theory (IRT) approach [graded response model (GRM)] and the Rasch model. Before running the GRM, IRT assumptions [unidimensionality (Loevinger's *H* coefficient), local dependence [*p*-values of G^2: adjusted for false discovery rate, FDR], and monotonicity [number of significant violations and *Crit* value]) were examined. Furthermore, item fits (assessed through S-χ^2 and its *p*-values [adjusted for FDR]) were assessed. In GRM, there are two parameters for items: in - slope/ discrimination parameter (α) and threshold/ difficulty parameters (b). For both parameters in GRM, local dependence and item fits were estimated using the R package *mirt* version 1.34. Unidimensionality and monotonicity were estimated through R package *mokkoen* version 3.0.6. In addition, IRT reliability was also calculated. In the Rasch model, infit mean square (infit MnSQ), outfit MnSQ, item difficulty, item and person separation index, and item and person reliability were estimated. Differential item functioning (DIF) bias across age, either having depression (PHQ-9 ≥ 10) or having anxiety (GAD-7 ≥ 10), estimated Mantel–Haenszel χ^2. SPSS version 21.0 (IBM, Armonk, NY), AMOS version 27 (IBM), JASP version 0.14.1.0 software (JASP Team, Amsterdam, Netherlands), Rasch analysis, and DIF were run through jMetrik version 4.1.1 (Psychomeasurement Systems, Charlottesville, VA), and RStudio (RStudio, Boston, MA) was used for statistical analysis.

TABLE 1 | Demographic characteristics of participants.

Variables	Mean ± SD, *n* (%)
Sex (male) (*N* = 260)	132 (50.8%)
Grade (*N* = 260)	
1st year	48 (18.4%)
2nd year	52 (20%)
3rd year	63 (24.2%)
4th year	34 (13.1%)
5th year	33 (12.7%)
6th year	21 (8.1%)
7th year	9 (3.5%)
Rating scale scores	
Stress and Anxiety to Viral Epidemics-6 items (SAVE-6)	13.3 ± 4.1 (4∼24)
Generalized Anxiety Disorder-7 items (GAD-7)	9.8 ± 3.7 (0∼20)
Patient Health Questionnaire-9 items (PHQ-9)	11.8 ± 5.7 (0∼27)

N, Total number of medical students; n, sample.
SD, standard deviation.

RESULTS

Population Characteristics

Among the 260 UNMSM medical students who participated in this study, 50.8% (132/260) were male; thus, the male/female ratio was 1.03. The participants' median age was 22 years (Q1: 20; Q3: 23.5). Most students (61.5%) had completed the first 3 years of medical school (163/260) (**Table 1**). The participants' mean rating scale results were 13.3 ± 4.1 (range: 4–24), 9.8 ± 3.7 (range: 0–20), and 11.8 ± 5.7 (range: 0–27) for SAVE-6, GAD-7, and PHQ-9, respectively (**Table 1**).

Factor Structure and Psychometric Properties of SAVE-6

Peruvian Spanish Version of SAVE-6

The distribution of six items of the Peruvian Spanish version of SAVE-6 was within the normal limit based on the skewness and kurtosis for an acceptable limit range of ±2 (**Table 2**). Sample adequacy and data suitability for conducting factor analysis were checked using the KMO measure of 0.80 and Bartlett's test of sphericity (p <.001). CFA had a good model fit [χ2 (df, *p*-value) = 13.290 (9, 0.150), CFI = 0.993, TLI = 0.988, RMSEA = 0.043, SRMR = 0.051, **Table 3**) for the single-factor model of SAVE-6. However, the factor loading value of item 5 was too low (0.251, **Table 2**).

Peruvian Spanish Version of SAVE-6 Excluding Item 5

Since the factor loading value of item 5 in the Peruvian Spanish version of SAVE-6 was too low, we checked the psychometric properties of the scale excluding item 5. The KMO measure of 0.80 and Bartlett's test of sphericity (p < 0.001) showed the sample was adequate and data were suitable for conducting factor analysis for SAVE-6 excluding item 5. CFA had improved good model fits (χ2 [df, *p*-value] = 7.183 (5, 0.207), CFI = 0.996, TLI = 0.992, RMSEA = 0.041, SRMR = 0.044, **Table 3**) for the single-factor structure model of SAVE-6 excluding item 5.

TABLE 2 | Factor structure of the Peruvian Spanish versions of SAVE-6 and SAVE-6 excluding item 5.

Items	Response scale					Descriptive				SAVE-6			SAVE-6 excluding item 5		
	0	1	2	3	4	M	SD	Skewness	Kurtosis	CITC	CID	Factor loading	CITC	CID	Factor loading
Item 1	2.7	15.8	40.4	30.8	10.4	2.30	0.948	−0.094	−0.306	0.565	0.738	0.620	0.541	0.811	0.603
Item 2	2.3	21.5	40.4	24.6	11.2	2.21	0.980	0.143	−0.524	0.624	0.723	0.737	0.742	0.752	0.745
Item 3	2.7	23.5	39.6	24.2	10.0	2.15	0.982	0.155	−0.516	0.710	0.700	0.848	0.667	0.775	0.855
Item 4	9.6	33.5	33.1	18.5	5.4	1.77	1.034	0.251	−0.495	0.536	0.745	0.642	0.583	0.801	0.653
Item 5	10.0	28.5	34.2	19.2	8.1	1.87	1.090	0.172	−0.585	0.228	0.824	0.251	-	-	-
Item 6	0.4	4.2	22.7	38.5	34.2	3.02	0.881	−0.550	−0.329	0.573	0.738	0.636	0.568	0.804	0.626

0 = never, 1 = rarely, 2 = sometimes, 4 = often, 5 = always.

M, mean; SD, standard deviation; CITC, corrected item-total correlation; CID, Cronbach's α if item deleted; CI, confidence interval; SAVE-6, Stress and Anxiety to Viral Epidemics-6 items.

Factor loading values of the items ranged between 0.603 and 0.855, Cronbach's α between 0.752 and 0.811, and corrected item-total correlations between 0.541 and 0.742 (**Table 2**). Multi-group CFA results (**Supplementary Table S1**) showed strict invariance of SAVE-6 excluding item 5 across sexes, in those with depression (PHQ-9 ≥ 10), and in those with anxiety (GAD-7 ≥ 10).

Reliability of SAVE-6 and SAVE-6 Without Item 5 and Evidence-Based on Relations to Other Variables

Peruvian Spanish Version of SAVE-6

The Peruvian Spanish version of SAVE-6 showed good internal consistency (Cronbach's $\alpha = 0.780$, McDonald's $\Omega = 0.792$) and good convergent validity based on Pearson's correlation coefficient with GAD-7 ($r = 0.252$, $p < .001$) and PHQ-9 ($r = 0.242$, $p < .001$) scores. The SAVE-6 score was significantly higher among participants with anxiety [GAD-7 ≥ 10, $t(258) = 14.719$, $p < .001$] and depression [PHQ-9 ≥ 10, $t(258) = 4.978$, $p < .001$].

Peruvian Spanish Version of SAVE-6 Excluding Item 5

The SAVE-6 showed good internal consistency (Cronbach's $\alpha = 0.820$, McDonald's $\Omega = 0.829$) and good convergent validity based on Pearson's correlation coefficient with GAD-7 ($r = 0.224$, $p < 0.001$) and PHQ-9 ($r = 0.217$, $p < .001$) scores when item 5 was excluded. The total score was significantly higher among participants with anxiety [GAD-7 ≥ 10, $t(258) = 13.144$, $p < 0.001$] and depression [PHQ-9 ≥ 10, $t(258) = 4.615$, $p < 0.001$].

Graded Response Model

Peruvian Spanish Version of SAVE-6

Information about IRT assumptions is presented in **Table 3** and **Supplementary Table S2**. Loevinger's H coefficient (0.412; **Table 3**) suggested that the Peruvian version of SAVE-6 was moderately unidimensional. Non-significant p-values of G^2 (**Supplementary Table S2**) suggested the absence of local dependency between items. The absence of significant violation and the low value of the *Crit* statistic (<40) for all items indicated that the monotonicity assumption was valid. Results regarding Loevinger's H coefficient, G^2, and monotonicity suggested the suitability to run an IRT model. **Supplementary Table S3** presents the item fit statistics of the Peruvian version of SAVE-6. After controlling the FDR, the p-values of S-χ^2 indicated that all items fit the scale well, which suggested that all the items belong to the scale. The slope/discrimination parameters (α) ranged between 0.472 and 4.031 (mean = 1.912) (**Supplementary Table S3**). Item 5 had a low slope, item 1 had a high slope, and the rest of the items had a very high slope. All items except item 5 provided reasonable information and were more efficient in discriminating among individuals assessed through the Peruvian version of SAVE-6. The threshold coefficients (b) in **Supplementary Table S3** suggested that a higher latent trait or theta was required to endorse Likert-type response options from "often" to "always" in all items except item 6. Threshold characteristics curves (**Figure 1A**) showed that curves for item 5 were very flat. This suggested the non-suitability of item 5.

Peruvian Spanish Version of SAVE-6 Excluding Item 5

Loevinger's H coefficient (0.536; **Table 3**) suggested that the Peruvian version of SAVE-6 was highly unidimensional, even when item 5 was excluded. Non-significant p-values of G^2 (**Supplementary Table S2**), the absence of significant violation, and the low value of the *Crit* statistic (<40) for all items (**Supplementary Table S2**) suggested that the local dependence and monotonicity assumption was valid. **Supplementary Table S3** presents the item fit statistics of the Peruvian version of SAVE-6 excluding item 5. After controlling the FDR, the p-values of S-χ^2 indicated that all items fit the scale well, which suggested that all the items belong to the scale. The slope/discrimination parameters (α) ranged between 1.327 and 4.173 (mean = 2.218) (**Supplementary Table S3**). Item 1 had a moderate slope, whereas the rest of the items had a very high slope. All items provided reasonable information and were more efficient in discriminating among individuals assessed through the Peruvian version of SAVE-6 excluding item 5. Item 1 provided the least information and item 3 provided the most information about the latent trait. The threshold coefficients (b) in **Supplementary Table S3** suggested that a higher latent trait or theta was required to endorse Likert-type response options: from "often" to "always" in all items except Item 6. **Figure 1B** presents the threshold characteristics curves of the Peruvian version of SAVE-6. **Supplementary Figure S1** shows the scale

TABLE 3 | Scale-level psychometric properties of the Peruvian Spanish versions of SAVE-6 and SAVE-6 excluding item 5.

Scales	SAVE-6	SAVE-6 excluding item 5	Suggested cutoff
Psychometric properties	**Scores**		
Floor effect	0	0	15%
Ceiling effect	0.8	1.5	15%
Mean inter-item correlation	0.382	0.484	Between 0.15 and 0.50
Cronbach's α	0.780	0.824	≥0.7
McDonald's *Ω*	0.792	0.829	≥0.7
Split-half reliability (odd-even)	0.793	0.789	≥0.7
Standard error of measurement	1.92	1.55	Smaller than SD (5.25)/2
Loevinger's *H* coefficients	0.412	0.536	-
Rho coefficient	0.788	0.864	≥0.7
IRT reliability	0.863	0.837	≥0.7
Item separation index	7.639	8.583	≥2
Person separation index	2.018	2.322	≥2
Item reliability	0.983	0.987	≥0.7
Person reliability	0.803	0.844	≥0.7
Statistics from exploratory factor analysis			
KMO measure of sample adequacy	0.80	0.80	0.50
Bartlett's test of sphericity	489.1955, $p < 0.001$	464.258, $p < 0.001$	Significant
Determinant	0.148	0.164	
Eigenvalue	3.03	2.95	1 or above
Variance	50.45	59.01	
RSMR	0.060	0.050	
TLI	0.888	0.900	
Output from parallel analysis			
Reduced eigenvalue	2.472	2.400	1 or above
95th percentile of random reduced eigenvalue	0.325	0.279	
Model fits of confirmatory factor analysis			
χ^2 (df, *p*-value)	13.290 (9, 0.150)	7.183 (5, 0.207)	Non-significant
CFI	0.993	0.996	>0.95
TLI	0.988	0.992	>0.95
RMSEA	0.043	0.041	<0.08
SRMR	0.051	0.044	<0.08

SAVE-6, Stress and Anxiety to Viral Epidemics-6 items; IRT, item response theory; KMO, Kaiser–Meyer–Olkin; RSMR, root-mean-square residual; TLI, Tucker–Lewis index; CFI, comparative fit index; RMSEA, root-mean-square-error of approximation; SRMR, standardized root-mean-square residual.

information curves of the Peruvian Spanish version of SAVE-6 and SAVE-6 excluding item 5. Both scales were good for assessing the latent trait between −2.5 and 2.0 theta levels. However, there were several peaks in both curves that might be due to polytomous data.

The Rasch Model

Peruvian Spanish Version of SAVE-6

Supplementary Table S4 presents the Rasch model outputs of the Peruvian version of SAVE-6. Infit and mean squares of all the items were between the recommended range (0.50–1.50) except item 5. Items 6 and 4 had the lowest and highest item difficulty, respectively.

Peruvian Spanish Version of SAVE-6 Excluding Item 5

Supplementary Table S4 presents the Rasch model outputs of the Peruvian version of SAVE-6 when item 5 was excluded. Infit and mean squares of all the items were within the recommended range (0.50–1.50). Items 6 and 4 had the lowest and highest item difficulty, respectively. DIF results (**Supplementary Table S5**) showed an absence of DIF bias in items across sexes, in those with depression (PHQ-9 ≥ 10), and in those with anxiety (GAD-7 ≥ 10).

DISCUSSION

In this study, we aimed to explore the psychometric properties of the Peruvian Spanish version of SAVE-6 among medical students in Peru. We observed that SAVE-6 was a reliable and valid rating scale, which could assess medical school students' pandemic-related anxiety. The CFA showed a good model fit for the single-factor model of SAVE-6. Multi-group CFA showed that the Peruvian Spanish version of SAVE-6 can measure medical students' pandemic-related anxiety in the same way across sexes and in students with depression (PHQ-9 ≥ 10) or anxiety (GAD-7 ≥ 10). It also showed good internal consistency and convergent validity with other anxiety scales, such as GAD-7 and PHQ-9.

In this study, we assessed the efficiency of the Peruvian Spanish version of SAVE-6 *via* GRM, a modern test theory model. Similar to the classic test theory, the unidimensionality test (Loevinger's *H* coefficient) confirmed the single-factor structure of both the Peruvian Spanish versions of SAVE-6 and SAVE-6 excluding item 5. The item fit values of SAVE-6 excluding item 5 confirmed that all items were included on the scale. Similar to the results of the factor analyses, item 5 of SAVE-6 had low slope parameters, and the threshold characteristic curves of this item were flat. However, all items of SAVE-6 excluding item 5 were sufficient to discriminate high scores from low scores. Both versions efficiently assessed the latent trait between −2.5 and 2.0 theta levels. The Rasch analysis infit and outfit MnSqs showed similar results of factor analysis and GRM, and item 5 had higher infit and outfit MnSqs than the recommended value (0.5–1.5). These outputs suggested the unsuitability of this item. In both versions, item 6 was the least difficult, and item 4 was the most difficult. Both versions had the acceptable item and person separation indices and reliability. DIF results suggested consistent results with multi-group CFA. There was an absence of DIF bias in items of the Peruvian version of SAVE-6 across sexes, in those with depression, and in those with anxiety.

However, we observed that the factor loading value of item 5 ("Are you worried that others might avoid you even after the infection risk has been minimized?") in the Peruvian Spanish version of SAVE-6 was too low (0.251) among medical students

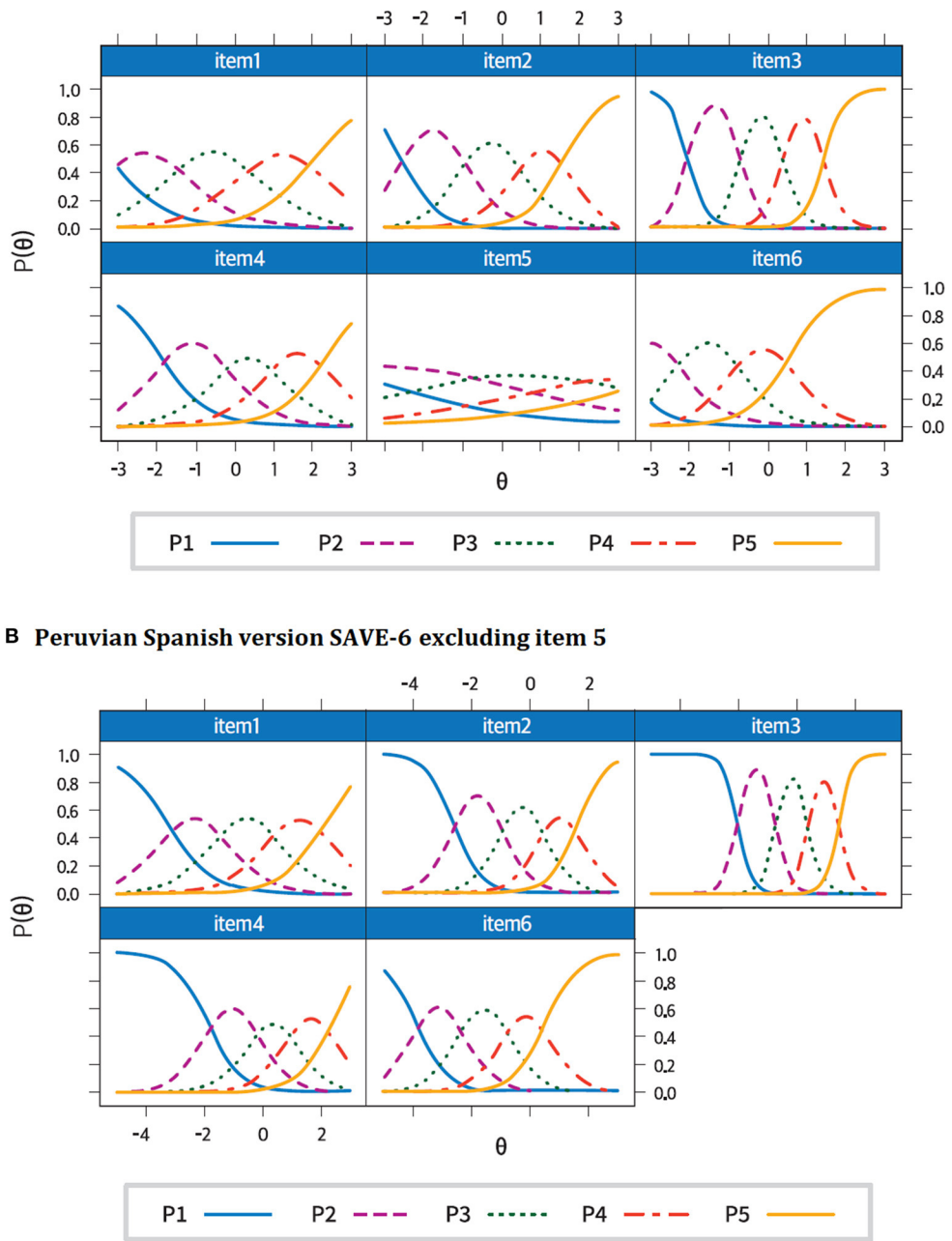

FIGURE 1 | Threshold characteristics curves of the Peruvian Spanish versions of SAVE-6 **(A)** and SAVE-6 excluding item 5 **(B)**. SAVE-6, Stress and Anxiety to Viral Epidemics-6 items.

in Peru. The reasons may be as follows. First, item 5 may not be useful to assess one's pandemic-related anxiety. Originally, SAVE-9 was clustered around two factors: pandemic-related anxiety (items 1, 2, 3, 4, 5, and 8) and work-related stress (items 6, 7, and 9). However, in Russia (41) and Germany (42), item 5 was not clustered around a pandemic-related anxiety subscale, but rather a work-related subscale, among a sample of healthcare workers. Therefore, we can speculate that item 5 can be useful in measuring the work-related stress of healthcare workers rather than anxiety in response to a viral epidemic. Second, a sampling of medical students, who may play a similar role to healthcare workers, may influence the results. Similar results were observed in a sample of healthcare workers in Spain (30). In this study, the factor loading value of item 5 was low (0.38). Thus, the validity of

the single-factor model of the Peruvian Spanish version of SAVE-6 needs to be checked in the general population. Third, cultural differences might influence the results. The clusters observed in studies conducted in Japan (43) and Turkey (44) were in parallel with the Korean study but differed in countries such as Russia and Germany. SAVE-6 showed a good fit for a single-factor model among the general populations of Korea (21), Lebanon (24), and the US (26). Further studies are needed to explore the differences in SAVE-6 clustering in other countries.

This study has some limitations. First, it was not possible to arrive at the previously calculated sample. However, the gap between the sample obtained and the one calculated is small (5.3% vs. 5%). Therefore, despite not being able to reach our target population sample, the results obtained from the psychometric validation process are reliable. In any case, we suggest corroborating these in various student populations. Additionally, there was heterogeneity in the percentages of students in each grade due to the poor response of students in the higher grades. Hence, this sample may not be representative of our population. This may have been due to the unavailability of Internet access or to the greater academic load that students in the final grades of medical school bear. However, we re-sent the survey over 4 weeks to reach as many participants as possible. Second, due to the current pandemic situation, face-to-face surveys have not been possible, and surveys had to be conducted online. Anonymous online surveys are likely to induce response biases. Third, the GAD-7 version applied in this study was not validated among medical students in Peru in Peruvian Spanish. We applied the European Spanish version of GAD-7, which might influence the results. Finally, the low factor loading value of item 5 might have come from the sampling issue, although we already compared the characteristics of item 5 among European countries. In the future, when SAVE-6 is applied to other samples, researchers should consider whether item 5 will be included or not.

In conclusion, the Peruvian Spanish version of SAVE-6 excluding item 5, rather than the full SAVE-6, can be applied to measure pandemic-related anxiety of medical students in Peru with good validity and reliability. In the current COVID-19 pandemic, this scale would be helpful in assessing the psychological problems of medical students.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical approval for all procedures and analyses conducted for the current manuscript was provided by the Research Ethics Committee of the Faculty of Medicine of UNMSM (application 0165). Electronic informed consent was obtained from all individual participants.

AUTHOR CONTRIBUTIONS

AL-R, NJ-M, FP-F, and BG contributed to the acquisition of data. SC, OA, VV-R, and CA-D contributed to the analysis and interpretation of data. All authors agreed to be accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved. All authors contributed substantially to the conception and design of the study and to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.876379/full#supplementary-material

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Is Brain-Derived Neurotropic Factor Methylation Involved in the Association Between Prenatal Stress and Maternal Postnatal Anxiety During the COVID-19 Pandemic?

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Background: The COVID-19 pandemic is a collective trauma that may expose susceptible individuals to high levels of stress. Pregnant women represent a high-risk population, considering that pregnancy is a period of heightened neuroplasticity and susceptibility to stress through epigenetic mechanisms. Previous studies showed that the methylation status of the *BDNF* gene is linked with prenatal stress exposure. The goals of this study were (a) to assess the association between pandemic-related stress and postnatal anxiety and (b) to investigate the potential role of maternal *BDNF* methylation as a significant mediator of this association.

Methods: In the present study, we report data on the association among pandemic-related stress during pregnancy, maternal *BDNF* methylation, and postnatal anxiety symptoms. Pandemic-related stress and postnatal anxiety were assessed through self-report instruments. *BDNF* methylation was estimated in 11 CpG sites in DNA from mothers' buccal cells. Complete data were available from 108 mothers.

Results: Results showed that pandemic-related stress was associated with an increased risk of postnatal anxiety, $r = 0.20$, $p < 0.05$. CpG-specific *BDNF* methylation was significantly associated with both prenatal pandemic-related stress, $r = 0.21$, $p < 0.05$, and postnatal maternal anxious symptoms, $r = 0.25$, $p = 0.01$. Moreover, a complete mediation by the *BDNF* CpG6 methylation emerged between pandemic-related stress during pregnancy and postnatal maternal anxiety, ACME = 0.66, $p < 0.05$.

Conclusion: These findings suggest that BDNF epigenetic regulation by pandemic-related stress might contribute to increase the risk of anxiety in mothers. Policymakers should prioritize the promotion of health and wellbeing in pregnant women and mothers during the present healthcare emergency.

Keywords: anxiety, *BDNF*, COVID-19, methylation, epigenetics, pandemic, pregnancy, stress

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INTRODUCTION

Pregnancy is a period of heightened neuroplasticity for women (1). Changes in brain connectivity and neuroendocrine regulation are meant to facilitate the transition to motherhood and to prepare the women to develop appropriate caregiving skills and attachment sensitivity to the newborn soon after delivery (2, 3). Nonetheless, this same heightened neuroplasticity may also result in increased susceptibility to adverse conditions and stressful exposures during pregnancy (4–6). The consequences of prenatal stress may be deleterious for women, and they may set the stage for a greater risk of developing anxious symptoms, which may impair not only maternal mental health but also the early establishment of an intimate and reciprocally satisfying relationship with the infant. Recent research suggests that environmental stress may alter epigenetic mechanisms—such as DNA methylation—at specific sites of genes involved in stress reactivity and regulation.

The COVID-19 pandemic is an unprecedented healthcare emergency and at the same time a prolonged and unpredictable collective trauma that has dramatically affected every domain of our life. The fear of contagion, the partial knowledge of the virus and its implications, together with the lockdown limitations that were key to the success of mitigation and containment strategies are sources of psychological distress that should not be underestimated in at-risk individuals. A recent meta-analytic study suggested that during the pandemic anxiety—rather than depressive—symptomatology may be heightened in pregnant and postpartum women (7). In the present study, we report on the association between pandemic-related stress experienced by women during pregnancy and maternal anxious symptoms after delivery. Moreover, we highlight the role played by the DNA methylation of a specific stress-related target gene—namely, the *BDNF* gene—in mediating this relationship.

Neuroplasticity and Stress Susceptibility During Pregnancy

During pregnancy, the neurobiology of mothers undergoes dramatic changes that involve regulatory processes occurring at the level of the central nervous system and different neuroendocrine axes (1). A great variety of intertwined functional and structural changes occurs in the female brain throughout pregnancy and may continue during the postpartum period. These neurobiological adaptations are meant to be largely informed by neuroendocrine and environmental triggers (8, 9). Specific brain areas in which variations in brain volume occur involve the medial preoptic area (mPOA) and the hippocampus (10, 11), brain areas that have well-known associations with the emergence of specific caregiving behaviors in both animal models and humans (12, 13). Mechanisms underlining the restructuring of the maternal brain across pregnancy involve neurogenesis, synaptic remodeling, and reshaping of dendrites (1, 14–16).

Such a general reconfiguration of maternal neurobiology has relevant implications for the susceptibility of pregnant women to stressful exposures. Indeed, as pregnancy is a time windows of increased interaction between genes and environmental exposures, it is also a critical period for regulation triggered by adverse and stressful conditions (17). Heightened risk of stress-related risk conditions has been highlighted in women exposed to adverse events during pregnancy (18, 19). Rates of postpartum anxiety range from 10 to 17% (20, 21) and anxious symptoms reported by mothers after delivery have often precursors in stress experiences during pregnancy (22). A history of stress and adverse conditions during pregnancy is one of the most significant antecedents of postnatal anxiety in mothers (23). Timely identification of prenatal risk and postnatal signs of maternal anxiety is crucial in clinical settings as untreated maternal anxiety may have a plethora of consequences for both women's later psychological adjustment to motherhood and child developmental trajectories (5, 24–28).

The Brain-Derived Neurotropic Factor Gene: An Epigenetic Target for Stress Exposure and Psychiatric Risk

Among the mechanisms involved in setting the risk for stress susceptibility during pregnancy, the epigenetic regulation of specific stress-related genes has been recently reviewed and confirmed (29). Behavioral epigenetics refers to alterations of the DNA function that are highly malleable in response to environmental exposures, that do not involve mutations of the dinucleotide sequence, and that can affect gene expression and protein synthesis (30). In other words, whereas the genome consists of the genetic information contained in the DNA that informs gene transcription and expression, the epigenome defines which genes of this repertoire are actually expressed (31). DNA methylation is by far the most investigated epigenetic mechanism in animal and human neurobehavioral studies. It occurs when a methyl group binds to specific 5′-cytosine guanine-3′ dinucleotides (i.e., CpG sites) and may contribute to reducing gene expression (i.e., gene silencing) (32). Adverse exposures occurring during specific temporal window of heightened neuroplasticity and susceptibility to stress may be especially capable of leaving epigenetic marks capable of contributing to the dysregulation of key physiologic, neuroendocrine, and neurobehavioral systems (33). Moreover, DNA methylation is of specific concern when it occurs at the level of stress-related genes that are known for their implications in behavioral, cognitive, and socio-emotional development as well as in the promotion of physical and mental health (34, 35).

The brain-derived neurotropic factor (*BDNF*) gene may be a specific target gene of interest that has shown to be susceptible to epigenetic regulation following stressful exposures (36) and to be significantly associated with increased risk of psychiatric disorders, including anxious symptomatology (37). *BDNF* is a member of the neurotrophic growth factor family. It contains 11 exons in humans, nine of which include promoters that regulate its expression (38, 39). A large variety of cells express the *BDNF* molecule in different tissues using different splice sites, leading to the formation of numerous *BDNF* transcripts variants (40). It plays key functions in the regulation of proliferation, growth, maintenance, and survival of specific target neurons during pregnancy and in postnatal life (41, 42). Like

other neurotrophins, *BDNF* is essential for the outgrowth and activity-dependent neuroplastic remodeling that occurs during pregnancy (43, 44).

Notably, the *BDNF* gene is susceptible to epigenetic regulation by environmental stimulations, and this may be especially true during time windows of heightened neuroplasticity like pregnancy (45, 46). Environmental challenges and threats occurring during pregnancy may affect *BDNF* methylation profiles both in the brain and in peripheral tissues, such as blood and buccal cells (46, 47). Increased *BDNF* methylation has been documented in response to adverse life conditions in central and peripheral tissues of both animal models and humans (48, 49) and similar trends in *BDNF* methylation have been reported between peripheral and central assessments (37). CpG sites located in different exons may show environmentally regulated changes in their methylation status; nonetheless, the specific CpG sites and loci of epigenetic regulation of the *BDNF* gene by environmental stress exposures only partially overlap among different studies (37, 40). Higher stress-related serum cortisol has been linked with concurrent reduction in *BDNF* serum expression during the second trimester of pregnancy (50).

Animal models suggest that variations in *BDNF* expression may be mirrored in impairments of learning, memory, and social behavior, including anxiety-like traits (51). Associations with stress-related mood disorders and anxiety have been also reported in humans assessing *BDNF* methylation in peripheral tissues, such as blood and saliva (36, 52–55). Notably, previous research mainly focused on the effects of prenatal stress on the regulation of the *BDNF* methylation status in the offspring, highlighting statistically significant positive associations (47, 56, 57). Despite the fact that stress-related increases in glucocorticoids during pregnancy have been found to be associated with a lower synthesis of maternal *BDNF* (58), little is known about the effects of stress during pregnancy on the epigenetic regulation of maternal *BDNF* and on the subsequent risk for mental health, such as anxiety symptomatology.

The Present Study

The COVID-19 pandemic is an unprecedented healthcare emergency that is challenging all the domains of our daily life. Its rapid spread and the lack of complete knowledge about the virus resulted in the employment of population-based behavioral strategies to contain and manage the contagion. As these strategies resulted in prolonged and repeated lockdown periods, psychological stress emerged as a non-negligible side effect of the pandemic on a global scale. As the exposure to stress is of particular concern during time windows of heightened neuroplasticity, we wondered whether and how this collective trauma was affecting the health of women and infants. As such, we launched the Measuring the Outcomes of Maternal COVID-19-related Prenatal Exposure (MOM-COPE) research project in April 2020. The MOM-COPE project is a multi-centric and prospective study that involves ten neonatal units in Northern Italy and that includes the collection of self-report, behavioral, and epigenetic correlates of pandemic-related stress during pregnancy and further health-related and development outcomes from birth to 12-month-age of the infant (59). In the present study, we report on the association among pandemic-related stress during pregnancy, maternal BDNF methylation, and postnatal anxiety symptoms. Our first goal was to assess the association between pandemic-related stress and postnatal anxiety. Based on the literature reviewed above, we hypothesized a positive and significant relationship, with mothers reporting higher prenatal stress showing also the greatest elevations in postnatal anxious symptoms. Our second goal was to assess the role of maternal BDNF methylation as a significant mediator of this association. As suggested by previous research in animal models and humans, we hypothesized that (a) higher prenatal pandemic-related stress would be associated with increased methylation of the BDNF gene and (b) such an altered epigenetic status would associate with greater reports of anxiety after delivery. As previous research did not univocally highlight specific candidate CpG sites, we explored this association by focusing on a CpG-rich locus in the promoter region of the BDNF gene.

MATERIALS AND METHODS

Participants

The MOM-COPE is a prospective and multi-centric cohort study that involves ten neonatal units in Northern Italy and is aimed at highlighting the behavioral and epigenetic consequences of prenatal pandemic-related stress during the COVID-19 emergency for maternal health and infants' development. The fully detailed description of this project is reported elsewhere (59). Here we report on a sample of 108 mothers with complete prenatal (T_0) and neonatal (T_1) data between May 2020 and February 2021. Mothers were included if at least 18-year-old, in the absence of prenatal and perinatal diseases or injuries, if they delivered at term (i.e., from 37 + 0 to 41 + 6 weeks of gestation), and if they were negative for COVID-19 at delivery. Mothers were not considered eligible to the study in presence of any maternal or infants' comorbidity.

Ethics

The study was approved on April, 8th 2020 by the Ethics Committees (protocol ID 20200037366) of the project lead institution (IRCCS Mondino Foundation, Pavia, Italy) and the participating hospitals. All the procedures were performed in accordance with the 2018 Declaration of Helsinki for studies conducted with human participants. All mothers provided informed consent to participate to the study.

Procedures

Mothers were first contacted at antepartum classes or immediately following the postpartum period. Socio-demographic and neonatal data were obtained from medical records. Within 48 h from delivery, the mothers filled in a first set of questionnaires to provide retrospective quantitative measures of prenatal COVID-19-related stress and present anxiety symptoms. Between 6 and 24 h, buccal cells were obtained from mothers to assess *BDNF* methylation.

TABLE 1 | Pandemic-related stress questionnaire.

	Pandemic-related stress (Response: 5-point Likert scale)
	During pregnancy. . .
1	How much worried were you about the risk of COVID-19 infection?
2	How much did you feel that your pregnancy was at risk due to COVID-19 pandemic?
3	How much did you fear for your health?
4	How much did you fear for your baby's health?
5	How much did you feel that you were losing confidence in your health?
6	How much did you feel you had lost faith in medicine?

TABLE 2 | Positions of the selected *BDNF* CpG sites human genome assembly GRCh37 (hg19).

CpG site #	**Position**
1	Chr11: 27,723,218–27,723,219
2	Chr11: 27,723,214–27,723,215
3	Chr11: 27,723,203–27,723,204
4	Chr11: 27,723,190–27,723,191
5	Chr11: 27,723,161–27,723,162
6	Chr11: 27,723,159–27,723,160
7	Chr11: 27,723,143–27,723,144
8	Chr11: 27,723,137–27,723,138
9	Chr11: 27,723,128–27,723,129
10	Chr11: 27,723,125–27,723,126
11	Chr11: 27,723,095–27,723,096

Measures

Sample Characteristics

Mothers self-reported socio-demographic characteristics (i.e., age, educational level, and occupational status), pandemic-related stress during pregnancy, and present anxious symptoms. Neonatal characteristics (i.e., gestational age, birth weight, head circumference, neonatal length, Apgar at minute 1, breastfeeding at birth, and mode of delivery) were collected from medical records.

Questionnaires

For pandemic-related stress, an *ad hoc* questionnaire was developed to target dimensions of stress specifically related to the present COVID-19 healthcare emergency (Items are reported in **Table 1**); a mean score was obtained, ranging from 1 (low) to 5 (high). Anxious symptoms were assessed using the State-Trait Anxiety Inventory (STAI-Y) (60), a well-validated questionnaire that includes 20 items and provides a global score ranging from 20 (low) to 80 (high). A STAI-Y score above 40 is usually index of clinically relevant elevations in anxious symptoms. Mothers were considered eligible to the study only if negative to SARS-CoV-2. Nonetheless, PCR testing could not exclude direct or indirect exposures to the virus that thus were explored with *ad hoc* items indicating whether they had symptoms reminiscent of COVID-19 in the previous months, whether their relatives or significant others were positive to the virus, as well as whether they were hospitalized in intensive care units and/or eventually died with COVID-19. The physical direct/indirect exposure to the COVID-19 virus was dichotomized as 0 (no exposure) and 1 (at least one direct or indirect exposure).

Brain-Derived Neurotropic Factor Methylation

Maternal buccal cells samples were collected using the OraCollect kit OC-175 (DNA Genotek, Ottawa, Canada) between 6 and 24 h from delivery. Methylation assessment was conducted according to previous validated procedures from this lab (61, 62). The genomic DNA was extracted following manufacturer's protocols and its quality was assessed using a Qubit fluorimeter (Invitrogen, Thermo Fisher Scientific, Waltham, Massachusetts, United States). The methylation status of 11 CpG sites in the *BDNF* gene promoter region (chr11: 27,723,096–27,723,219; see **Table 2** for CpG-specific positions) was assessed by PCR amplification of bisulfite-treated DNA followed by Next Generation Sequencing (NGS) on a NEXTSeq-500 (Illumina, San Diego, California, United States). The region was selected based on previous research on the association of *BDNF* methylation with maternal mental health and stress (46). **Figure 1** illustrates the study methodology.

Plan of Analysis

Variables of interest (pandemic-related stress, anxious symptoms, and CpG-specific *BDNF*% methylation) were first tested for normal distribution. Kurtosis and asymmetry were within the ± 2 range and no outliers (values over ± 3 standard deviations from the mean) were detected. The presence of significant differences in variables of interest by exposure to the COVID-19 virus was tested with independent-sample *t*-tests. Separate Pearson's bivariate correlations were used to assess the presence of significant associations among pandemic-related stress during pregnancy, maternal anxious symptoms after delivery, and CpG-specific *BDNF*% methylation. Multiple-testing bias was checked using the Benjamini-Hochberg procedure, $q < 0.05$. CpG-specific *BDNF*% methylation values for which a significant association emerged with both pandemic-related stress and anxious symptoms were subsequently tested in a mediation model to assess their role as significant mediators of the relationship between pandemic-related stress and maternal anxious symptoms. The model was tested using R (version 4.0.0) (63) mediation package (64). A *post hoc* power analysis setting medium size effect, *alpha* = 0.05, and sample size 108 revealed an adequate power of 0.89. The statistical analyses were carried setting $p < 0.05$.

RESULTS

The socio-demographic descriptive statistics for the sample are reported in **Table 3**. The Cronbach alpha for the pandemic-related stress questionnaire was 0.83, suggesting a satisfactory internal consistency. All items loaded on a single factor solution with loadings above 0.72. Thirty-four mothers (32%) reported STAI-Y scores higher than the clinical cut-off. No statistically significant differences emerged for pandemic-related stress

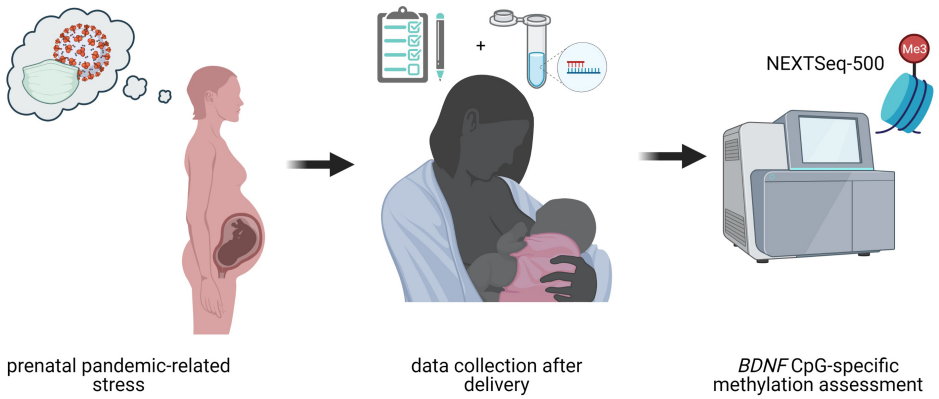

FIGURE 1 | Methodology of the study.

TABLE 3 | Descriptive statistics.

	Min	Max	Mean	SD
Gestational age (weeks)	37.00	42.00	39.71	1.05
Birth weight (grams)	2430.00	4345.00	3342.88	413.82
Apgar at minute 1	6.00	10.00	9.18	0.69
Maternal educational level (years of study)	5.00	23.00	14.44	3.57
			N	%
Infant's sex (females)			55	50.9
Delivery (eutocic)			69	63.9
Maternal occupational status (employed)			95	88.0

TABLE 4 | Comparison between mothers with and without any direct or indirect exposure to the COVID-19 during pregnancy for variables of interest.

	Exposure to the COVID-19 virus					
	No (n = 59)			Yes (n = 49)		
	Mean	SD	ES	Mean	SD	ES
Pandemic-related stress	2.34	0.62	0.08	2.54	0.70	0.10
Anxious symptoms	35.68	9.86	1.28	34.61	9.58	1.37
BDNF CpG-specific% methylation						
CpG 1	1.31	0.61	0.08	1.34	0.48	0.07
CpG 2	0.46	0.22	0.03	0.54	0.25	0.04
CpG 3	0.54	0.24	0.03	0.58	0.28	0.04
CpG 4	0.32	0.14	0.02	0.37	0.18	0.03
CpG 5	0.69	0.35	0.05	0.81	0.64	0.09
CpG 6	0.51	0.24	0.03	0.52	0.19	0.03
CpG 7	0.57	0.27	0.04	0.57	0.27	0.04
CpG 8	0.66	0.31	0.04	0.67	0.29	0.04
CpG 9	0.69	0.33	0.04	0.69	0.30	0.04
CpG 10	0.93	0.36	0.05	0.88	0.33	0.05
CpG 11	0.73	0.36	0.05	0.74	0.27	0.04

during pregnancy, maternal anxious symptoms post-delivery, and *BDNF* promoter region CpG-specific% methylation values between individuals with or without any direct/indirect exposure to the COVID-19 virus (**Table 4**).

A significant correlation emerged between pandemic-related stress and postnatal maternal anxious symptoms, $r = 0.20$, $p < 0.05$. The associations of *BDNF* CpG-specific% methylation values with pandemic-related stress during pregnancy and postnatal maternal anxious symptoms are reported in **Figure 2**. Pandemic-related stress was significantly correlated with CpG sites 4 ($r = 0.20$, $p = 0.037$), 6 ($r = 0.21$, $p = 0.027$), and 11 ($r = 0.20$, $p = 0.040$). Anxious symptoms were significantly correlated with CpG sites 2 ($r = 0.21$, $p = 0.027$), 3 ($r = 0.21$, $p = 0.026$), 6 ($r = 0.25$, $p = 0.011$), and 10 ($r = 0.28$, $p = 0.003$). All significant associations survived Benjamini-Hochberg check.

As *BDNF* CpG6 showed significant associations with both prenatal pandemic-related stress and postnatal maternal anxious symptoms, the methylation value at this CpG site was tested in the mediation model (**Figure 3**). A complete mediation by *BDNF* CpG6% methylation emerged (ACME = 0.66, 95% C.I. (0.00, 1.83), $p < 0.05$; ADE = 2.19, 95% C.I. (−0.55, 4.89), $p > 0.10$.

DISCUSSION

In this study, we were interested in investigating the association between prenatal pandemic-related stress experienced by women during the COVID-19 healthcare emergency and the levels of anxious symptoms reported after delivery. Moreover, we wanted to assess the role played by the methylation status of the *BDNF* promoter region in mediating this association, as previous research suggested that this gene might be susceptible to epigenetic regulation by adverse conditions occurring during pregnancy. Our findings are consistent with previous literature, suggesting that increased methylation of this gene may be involved in setting the risk for heightened anxious symptoms in mothers who experienced greater pandemic-related stress during gestation.

First, this effect seems to be independent of the actual exposure of women to the SARS-CoV-2 virus. In the present sample, we excluded women who tested positive for the COVID-19 by PCR assessment during pregnancy or at delivery. Moreover, we asked women to report any symptoms that could be reminiscent of COVID-19 disease as well as the presence of family members

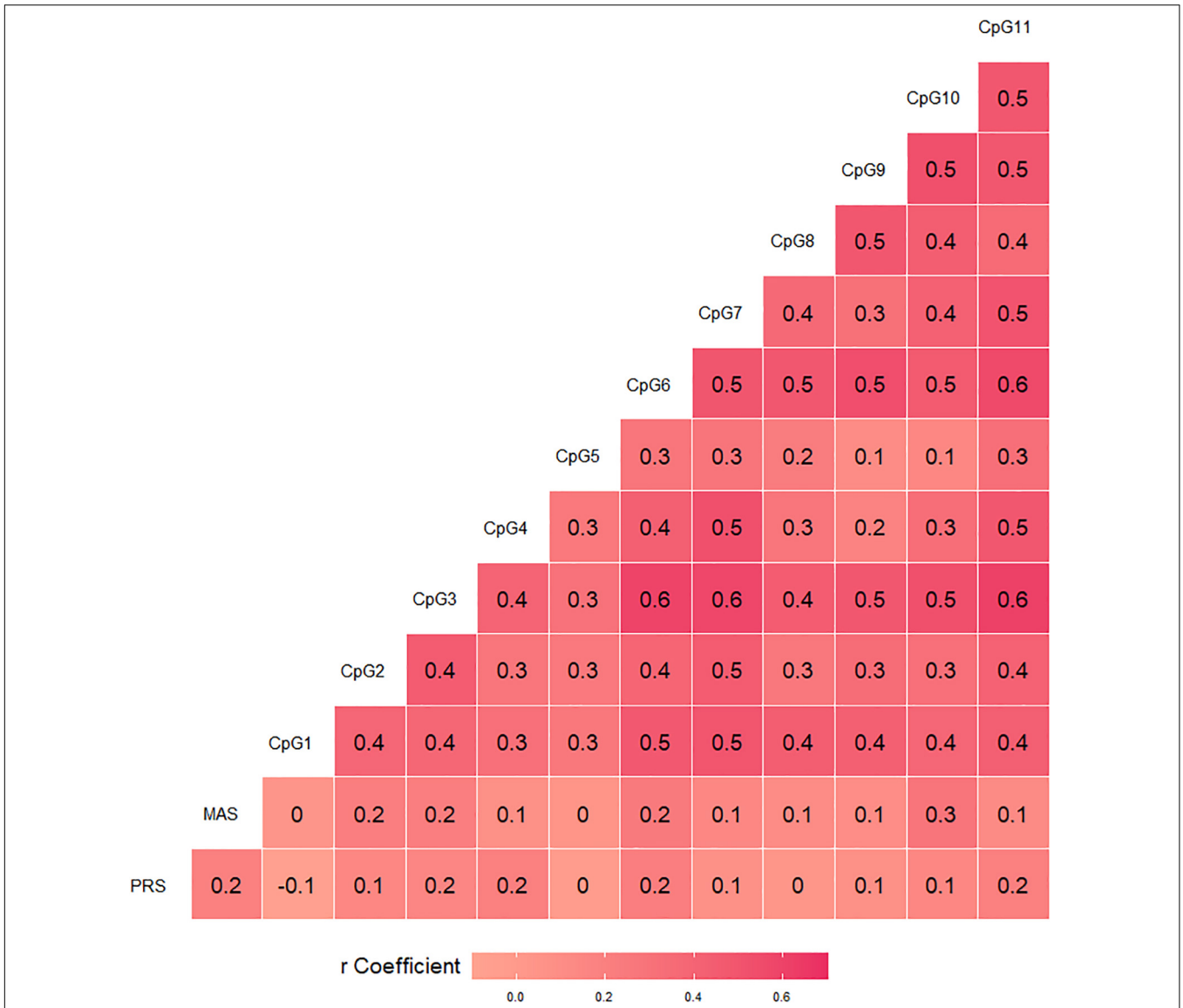

FIGURE 2 | Bivariate correlations of *BDNF* CpG-specific percentage methylation with pandemic-related stress (PRS) during pregnancy and postnatal maternal anxious symptoms (MAS).

or significant others who were positive, had been hospitalized, or died with COVID-19 when they were pregnant. As we compared women with or without any direct or indirect exposure to the SARS-CoV-2, no significant differences emerged for prenatal pandemic-related stress nor anxious symptoms assessed postnatally. As such, it is plausible to speculate that direct or indirect exposure to COVID-19 did not increase the risk of mental health problems in women during the COVID-19 pandemic. This is noteworthy for clinical practice, as healthcare professionals should not consider the presence of COVID-19 diagnosis as a risk factor for pandemic-related mental health risk and a broader preventive approach should be adopted. Indeed, pregnancy is a period of heightened neuroplasticity for women (1) and this may increase future mothers' susceptibility to stressful exposures (65). From this perspective, policymakers and healthcare professionals should be aware that pregnant women may be a specific at-risk population during a global pandemic, as they might be exposed to high levels of stress and risk of anxious symptomatology independently from the actual positivity to the virus.

Second, prenatal pandemic-related stress emerged as significantly associated with post-natal anxious symptoms in this sample. This finding confirms previous literature that already demonstrated how high levels of prenatal stress might predispose women to mental health problems after delivery (23). Nonetheless, the percentage of mothers reporting elevations in the standardized anxiety scale was well above (32%) previous reports on similar community samples (i.e., 10–17%) (20,

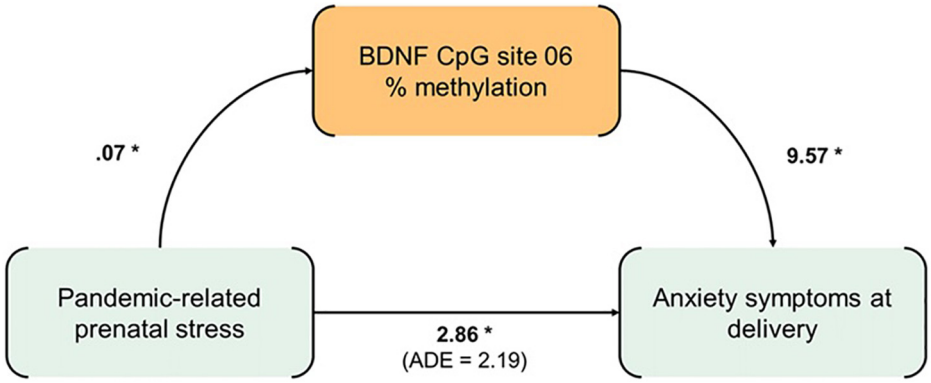

FIGURE 3 | Mediation model. *$p < 0.05$.

21). As such, during the present healthcare emergency, this heightened risk for impaired mental health for mothers should not be underestimated. The mental health risk connected to pandemic-related stress may act as a silent pandemic that is relatively independent of SARS-CoV-2 direct or indirect exposure and that may have critical consequences for mothers' wellbeing. Moreover, previous research has shown that high levels of maternal anxiety after delivery may be a trigger condition for further negative health consequences for mothers as well as for their infants (66). For example, evidence from the Generation R study suggested that mothers with high levels of postnatal anxiety had a higher probability to have infants with difficult temperament characterized by increased motor activity and negative emotionality (67). More recently, regulatory problems have been identified in infants of mothers with elevated levels of postnatal anxiety (68). Moreover, infants of mothers with high levels of anxiety may also develop socio-cognitive problems, such as attention bias toward threat-related stimuli (69). Recognizing, targeting, and taking care of pandemic-related stress with appropriate preventive and dedicated healthcare strategies should be a priority goal of policymakers and clinicians during the time of pandemic we are living in order to promote better maternal health and to prevent long-term detrimental consequences for children development.

Third, higher levels of CpG-specific *BDNF* methylation in the promoter region were found to be significantly associated with both prenatal pandemic-related stress (27% of assessed CpG sites) and maternal post-delivery anxious symptoms (36% of assessed CpG sites). The *BDNF* gene is well-known to be involved in neuroplasticity processes that occur during pregnancy and that constitutes part of the biological communications occurring between the maternal and the fetal compartments (43). Not surprisingly, the *BDNF* regulation has been previously found to be susceptible to stressful exposures occurring during pregnancy (45, 47). It has also been shown that the epigenetic regulation of the *BDNF* gene may be involved in setting the risk for psychiatric and affective disorders, such as depression and anxiety (36, 53). In our sample, a specific CpG site (CpG6; chr11-27,723,190–27,723,191) emerged as a significant mediator of the relationship between pandemic-related stress and post-partum maternal anxiety. This CpG site is included in one of the promoter regions of the *BDNF* gene previously highlighted by Kertes et al. (46) to be plausible loci of epigenetic regulation in relation to both maternal adversity exposure and postnatal mental health issues, including anxiety-related outcomes. This finding suggests that epigenetic regulation of *BDNF* gene by adverse events occurring during pregnancy may play a causal role in contributing to increased risk of maternal anxious symptoms after delivery.

Of course, it should be highlighted that *BDNF* is only one of the genes involved in the risk of affective symptomatology in pregnant women and mothers. Previous research reported on different stress-related genes, including—among others—*BDNF*, but also *SLC6A4* (35, 70), *NR3C1* (33, 71), and *FKBP5* (72). It is possible that the epigenetic regulation occurring at multiple target sites may interact in producing higher rates of mental health risk in pregnant women and mothers and this should be tested in future studies with larger samples that will eventually provide the opportunity to conduct epigenome-wide assessments. Although previous research suggests a global trend in similar methylation levels of *BDNF* assessed in central and peripheral tissues (37), it should be recognized that the actual expression of *BDNF* variants may be under the control of a large number of splices and thus tissue-related differences cannot be excluded (40). We further recognize additional limitations of this study. Although the MOM-COPE is a longitudinal project, the data reported in the present study are cross-sectional and this limits the possibility to draw valid conclusions about the causal directions of associations. We assessed pandemic-related stress with an *ad hoc* self-report questionnaire that was developed to be sensitive to the specific nature of this unprecedented healthcare emergency. The obtained measure is retrospective. Although this may limit the generalizability of these findings, the concordance of our results with previous studies on the association of prenatal stress and maternal anxiety may indirectly corroborate the goodness of our *ad hoc* tool. The Pearson's bivariate correlation indexes reported are significant, but the

strength of the association of *BDNF* CpG-specific% methylation with pandemic-related stress and anxiety symptoms is mild. As such, it is largely possible that other factors may be involved; notably, we did not include women who tested positive for SARS-CoV-2 during pregnancy and we did not collect information on previous stressful or traumatic events that occurred during women's life. As such, we cannot exclude that additional previous adverse experiences may have already contributed to increased stress susceptibility in these women. In our study, only a specific *BDNF* CpG site was significantly associated with both prenatal pandemic-related stress and postnatal maternal anxious symptoms and was therefore investigated as a mediator. The biological relevance and plausibility of a single CpG site may be controversial; still, it might inform future research questions on the epigenetic mechanisms involved in short- and long-term impact of pandemic-related stress in vulnerable populations.

CONCLUSION

In sum, this study provides for the first time evidence of the role played by epigenetic regulation of the *BDNF*—a target gene that has known implications in prenatal stress and psychiatric disorders—in setting the risk of less-than-optimal mental health in pregnant women during the COVID-19 pandemic. These findings have specific implications for scientific advances as well as for healthcare professionals and policymakers. First, the present study contributes to the emerging literature on the behavioral epigenetic vestiges of prenatal stress exposure suggesting that a potential mediation pathway involving increased methylation of the *BDNF* gene may be involved in setting the stage for heightened maternal anxiety soon after delivery. Second, with these findings, we highlight the presence of a hidden and silent pandemic that is relatively independent of the actual positivity to the SARS-CoV-2 virus, but that is likewise risky for mothers' mental health. Investing in appropriate and timely care solutions for pregnant women and mothers during a time of pandemic should be a priority for perinatal healthcare professionals. Policymakers have the opportunity to strengthen existing services and to promote the development of new actions that prioritize the promotion of health and wellbeing in pregnant women and mothers during the present healthcare emergency.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics committee Pavia. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LP and RB: conceptualization. LP and RGio: methodology. LP, RGio, MV, FM, and AC: formal analysis. GB, LD, BG, RGia, MM, RN, CP, FP, EB, and BS: data collection. MV, FM, AC, and SG: data curation. LP and SG: writing—original draft preparation. RGio, MV, FM, and AC: visualization. SO and RB: supervision. LP: project administration and funding acquisition. All authors have read and agreed to the published version of the manuscript.

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The course and determinants of post-traumatic stress over 12 months after hospitalization for COVID-19

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Objective: To assess the trajectory of symptoms and symptom-defined post-traumatic stress disorder (PTSD) from 1.5 to 12 months after hospitalization for COVID-19 and determine risk factors for persistent symptoms and PTSD.

Methods: This was a prospective cohort study of consecutive patients discharged after hospitalization for COVID-19 before 1 June 2020 in six hospitals in Southern Norway. Symptom-defined PTSD was assessed by the post-traumatic stress disorder (PTSD) checklist for DSM-5 (PCL-5) at 1.5, 3 and/or 12 months after hospitalization, using DSM-5 criteria. Changes in PCL-5 symptom score and the prevalence of PTSD were analyzed with multivariable mixed models.

Results: In total, 388 patients were discharged alive, and 251 (65%) participated. Respondents had a mean (SD) age of 58.4 (14.2) years, and 142 (57%) were males. The prevalence of symptom-defined PTSD was 14, 8, and 9% at 1.5, 3, and 12 months, respectively. WHO disease severity for COVID-19 was not associated with PCL-5 scores. Female sex, lower age and non-Norwegian origin were associated with higher PCL-5 scores. The odds ratio (OR) (95%CI) for PTSD was 0.32 (0.12 to 0.83, $p = 0.019$) at 3 months and 0.38 (0.15 to 0.95, $p = 0.039$) at 12 months compared to 1.5 months. There was no association between PTSD and WHO severity rating.

Conclusions: The level of PTSD symptoms decreased from 1.5 to 3 months after hospitalization, but did not decrease further to 12 months, and there was no association between PTSD symptoms and COVID-19 disease severity.

KEYWORDS

post-traumatic stress disorder (PTSD), COVID-19, PCL-5 questionnaire, cohort, follow-up, medium-term

Introduction

Post-traumatic stress disorder (PTSD) is a chronic and debilitating mental condition that may develop in response to traumatic events that involve a life-threatening component, including acute medical diseases. A meta-analysis reported that 17–44% of critical illness survivors reported clinically important PTSD symptoms, and that symptoms of PTSD were associated with pre-ICU psychopathology, but not with age, disease severity, or ICU length of stay (1).

During the severe acute respiratory syndrome (SARS) outbreak in 2002–2004, many recovered SARS patients showed symptoms of PTSD at 1 and 3 months after discharge from hospital, and 4–5% satisfied the criteria for PTSD (2), although higher rates have been reported (3). Furthermore, the level of hypoxia is associated with PTSD symptoms (2). The prevalence of PTSD 12 months after hospitalization for the Middle East respiratory syndrome (MERS) were even higher, with 24% reporting severe or very severe PTSD (4).

Patients hospitalized for COVID-19 are characterized by fever, cough, dyspnea, chest pain, or confusion, and typically 10–20% of hospitalized patients have critical illness requiring care in the intensive unit (5, 6). Until June 2022, cumulatively 15.8% of patients hospitalized for COVID-19 in Norway required ICU care (7).

Recent studies have reported significant PTSD symptoms during and after hospitalization for COVID-19 among 2–40 % of patients with follow-up of 1–6 months, and just recently 12–15 months, in cross-sectional or cohort studies (8–20). Prevalence rates vary according to time after acute COVID-19, assessment method, sample selection, and geographical region. During follow-up, female sex and continued symptoms, but not age or disease severity, were associated with PTSD (20).

To understand the course of stress reactions, repeated measurements of PTSD symptoms during the convalescence of COVID-19 and longer observation times are necessary (9, 17). This study investigated the course of symptoms of PTSD over 12 months after COVID-19 onset, focusing on the change in symptoms and possible association with disease severity.

Materials and methods

Design and population

This was a multicenter study, inviting patients 2–6 weeks after discharge from six major hospitals in Norway after COVID-19, before 1 June 2020. All patients >18 years of age with a discharge diagnosis (International Statistical Classification of Diseases and Related Health Problems 10) of U07.1, U07.2, or J12.x were eligible. Among all 454 survivors, we excluded 15 patients living outside the hospitals' catchment areas, 13 unable to provide informed consent, and 38 participating in a conflicting COVID-19 treatment trial. In total, 251 (65%) of 388 eligible patients provided data for this study.

The Regional Committee for Medical and Health Research Ethics, Health Region South East (no. 2020/125384) and data protection officers at participating centers approved the study. Written informed consent was obtained by mail or a secure web-form. The study is registered with ClinicalTrials.gov (NCT04535154).

Data collection

As this was an observational study, clinical treatment was up to each hospital. However, during the study follow-up visits, we used a standard protocol.

Data were collected at four time points: (i) Previous medical history and data during COVID-19 hospitalization were extracted from the electronic medical records (EMR); (ii) about 1.5 month after hospitalization, participants responded to a paper or on-line questionnaire; all participants returned to the respective hospitals' outpatient clinics for a visit, including self-completed questionnaires at (iii) 3 and (iv) 12 months after hospitalization.

Demographics, clinical variables, and comorbidity

Basic demographics, symptoms, Charlson's comorbidity index (21), and severity of COVID-19 were extracted from the EMR by study physicians/nurses. COVID-19 severity was classified using a WHO ordinal severity score (22): 3 no oxygen supplementation, 4 oxygen supplementation, 5 high-flow oxygen or non-invasive ventilation, or 6–7 mechanical ventilation. We obtained supplementary information on socio-demographics, height, weight, and smoking history by self-report at the 3-month visit.

Assessment of PTSD

Symptoms of PTSD were assessed using a Norwegian version of the PCL-5 (PTSD Checklist for DSM-5) questionnaire (23). The PCL-5 contains 20 items on an ordinal scale (0 to 4), which are summed to a total score (range 0–80, with 80 denoting maximal symptoms). The PCL-5 also has an alternative scoring algorithm fitted to the five clusters of the DSM-5 PTSD criteria (24). We used the DSM-5 criteria scoring to define symptom-defined PTSD.

Statistical analyses

We analyzed data from respondents with at least one response to PCL-5 ($n = 251$). Descriptive statistics are presented as mean (SD), median (25th to 75th percentile) or number (%). We present PTSD symptoms as continuous scores on the PCL-5 total scale and the prevalence of PTSD using DSM-5 scoring.

We conducted longitudinal analyses using mixed models, thereby accounting for missing values and enabling us to use all available data. For PCL-5 total scores, we used a linear mixed model with random effect (intercept) at the patient level, and an unstructured covariance structure. The model was fitted using maximum likelihood. Because the distribution of PCL-5 total score was highly skewed with many subjects having a score of 0, we tried log and square-root transformations of the PCL-5 total scores. However, this did not improve the distribution of the residuals or the model fit. Therefore, we used untransformed values as the dependent variable and bootstrapping with 10,000 iterations to estimate 95% confidence intervals and *p*-values. We included independent variables selected *a priori*: occasion (1.5, 3, or 12 months), age (per year), sex (male vs. female), living alone (married/cohabiting vs. single/divorced/widowed), born in Norway (yes vs. no), education (university level vs. lower level), Charlson comorbidity score (0, 1, ≥2), and WHO ordinal severity score (3, 4, 5–7).

Adding a random effect at the hospital level to the model only marginally influenced the coefficients and did not alter the results. The intraclass correlation coefficient (ICC) at the hospital level was only 0.029 compared to 0.657 at the patient level. Therefore, we omitted the hospital level in further analysis. In a supplementary analysis, we repeated the linear mixed models for PCL-5 total scores with the same approach and the same variables.

PTSD was analyzed using a logistic mixed model, with random effect (intercept) at the patient level, and an unstructured covariance structure. Here we only used occasion (1.5, 3, or 12 months) and WHO ordinal severity score as covariates, because of the low number of events.

We used Stata version 17.0 (Stata Corporation, College Station, TX) or R (The R Foundation for Statistical Computing) for all statistical analyses. We chose a 5% significance level.

Results

The participants had a mean age of 58.4 years, range 16.6 to 91.3 years. Overall, 35/142 men (25%) and 13/109 women (12%) had been admitted to the ICU. Further demographic and clinical characteristics of the participants are shown in Table 1.

The mean (SD) PCL-5 total scores were 14.2 (14.2), 11.2 (12.9), and 10.4 (12.4) at 1.5, 3, and 12 months, respectively. Symptom-defined PTSD was present in 27 (14%), 18 (8%), and

TABLE 1 Descriptive statistics for respondents ($N = 251$), number (%) unless otherwise stated.

	n	
Age (years), mean (SD)		58.4 (14.2)
Sex, male		142 (57)
Education, university level (>13 years)	236	129 (55)
Norwegian origin	226	163 (72)
Smoking status, current/previous		121 (48)
Living alone (unmarried/divorced/widowed)	226	62 (27)
Body mass index (kg/m2), mean (SD)	235	28.2 (4.6)
Comorbidity		
Myocardial infarction		14 (6)
Congestive heart failure		11 (4)
Peripheral vascular disease		4 (2)
Cerebrovascular accident or transitory ischemic attack		6 (2)
Dementia/chronic cognitive deficit		0 (0)
Chronic obstructive pulmonary disease		8 (3)
Connective tissue disease		3 (1)
Peptic ulcer disease		13 (5)
Liver disease, incl cirrhosis		3 (1)
Diabetes		21 (8)
Hemiplegia		0 (0)
Moderate to severe chronic kidney disease, on dialysis, or transplant		7 (3)
Solid tumor		10 (4)
Leukemia		2 (1)
Lymphoma		0 (0)
AIDS		0 (0)
Charlson comorbidity index, weighted, mean (SD)		0.49 (0.99)
Charlson comorbidity index		
0		180 (72)
1		41 (16)
≥2		30 (12)
Status at hospital admission		
Systolic blood pressure (mmHg), mean (SD)	247	134 (18.4)
Diastolic blood pressure (mmHg), mean (SD)	247	78.3 (11.4)
Body temperature (°C), mean (SD)	244	37.6 (1.1)
Pulse rate (per min), mean (SD)	245	85.6 (19.2)
Respiratory rate (per min), mean (SD)	240	23.9 (8)
Arterial blood gas at admission		
pH, mean (SD)	220	7.46 (0.05)
P_aO_2 (kPa), mean (SD)	222	9.9 (2.2)
P_aCO_2 (kPa), mean (SD)	222	4.4 (0.9)
WHO severity rating		
3 Hospitalized, no oxygen therapy		87 (35)
4 Oxygen by mask or nasal prongs		121 (48)
5 Non-invasive ventilation or high-flow oxygen		10 (4)
6 Intubation and mechanical ventilation		32 (13)
7 Ventilation + ECMO		1 (0)

(Continued)

TABLE 1 Continued

	n	
NEWS2 score at admission	234	3.9 (2.6)
Admission to intensive care unit		48 (19)
Times and length of stay (days), median (25th to 75th percentile)		
Hospital length of stay	249	6 (3 to 11)
Length of stay in intensive care unit	46	10.5 (5 to 15)
Time from hospital admission to response		
Survey 1 (1.5 months)*	192	46 (29.5 to 56.5)
Survey 2 (3 months)*	173	97 (84 to 119)
Survey 3 (12 months)*	168	386 (358.5 to 406)

*Only for respondents in the respective surveys.
ECMO, extracorporeal membrane oxygenation.

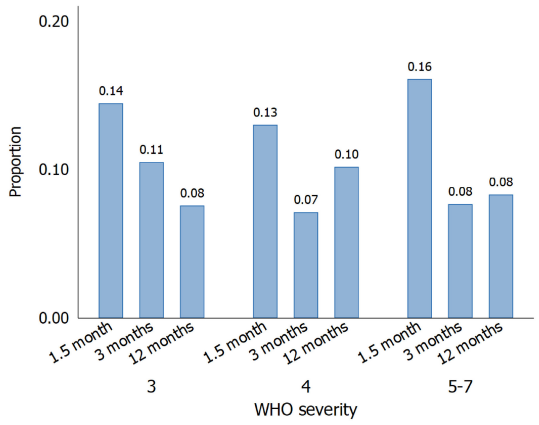

FIGURE 1
Proportions of hospitalized COVID-19 patients with symptom-defined PTSD (DSM-5 scoring) over time, according to WHO disease severity: 3, no oxygen requirement ($n = 87$); 4, oxygen by mask or nasal prongs ($n = 121$); 5–7, high-flow oxygen, non-invasive ventilation or intubation/mechanical ventilation ($n = 43$).

TABLE 2 Predictors of PCL-5 total symptom score, multivariable linear mixed model (n =565 observations, 225 patients).

Fixed effects	Coef.**	95% Conf. interval	*P*
Occasion			
1.5 months*	0		
3 months	−3.64	(−5.30 to −1.98)	<0.001
12 months	−3.76	(−5.51 to −2.01)	<0.001
WHO severity rating			
3* No oxygen use	0		
4 Oxygen use	0.82	(−0.68 to 2.32)	0.29
5–7 High flow, ventilatory support	1.06	(−1.15 to 3.27)	0.35
Sex			
Female*	0		
Male	−5.90	(−7.49 to −4.31)	<0.001
Age, per year	−0.07	(−0.13 to −0.02)	0.008
Education			
Lower level*	0		
University level	1.17	(−0.37 to 2.71)	0.138
Marital status			
Married/cohabiting*	0		
Single/divorced/widowed	1.14	(−0.50 to 2.77)	0.174
Norwegian origin?			
Yes*	0		
No	7.83	(5.79 to 9.88)	<0.001
Charlson comorbidity index			
0*	0		
1	2.76	(0.74 to 4.78)	0.007
≥2	0.15	(−2.04 to 2.35)	0.89
Random effects	SD		
Participant (intercept)	10.03		
Residual	6.78		
Model statistics			
Intraclass correlation coefficient	0.686		
Akaike's information criterion	4306.8		
Marginal/conditional R^2	0.149/0.733		

* Baseline category.
** Unstandardized beta coefficient.

19 (9%) of the patients at the same time points, but there was no association with disease severity (Figure 1).

In multivariable analysis of continuous PCL-5 scores, 3-month and 12-month scores were lower than 1.5-month scores, but there was no association with COVID-19 severity (Table 2, Figure 2). However, female gender, non-Norwegian origin, and lower age were associated with increased PCL-5 total scores.

Stratified analysis according to sex, showed a similar development in PTSD symptoms over time for men and women, and more PTSD symptoms with non-Norwegian origin (Supplementary Table 1). However, the results for educational level seemed inconsistent, with more symptoms with higher education among women, but less symptoms with higher education among men. Being single/divorced was associated with more symptoms only among men. Finally, the association for Charlson comorbidity index was different for men and women, with score ≥2 being associated with less PTSD symptoms only among men.

The multivariable logistic model ($n = 618$ observations, 221 patients) showed odds ratios (OR) (95%CI) for PTSD of 0.32 (0.12 to 0.83, $p = 0.019$) at 3 months and 0.38 (0.15 to 0.95, $p = 0.039$) at 12 months compared to 1.5 months, and 0.93 (0.26

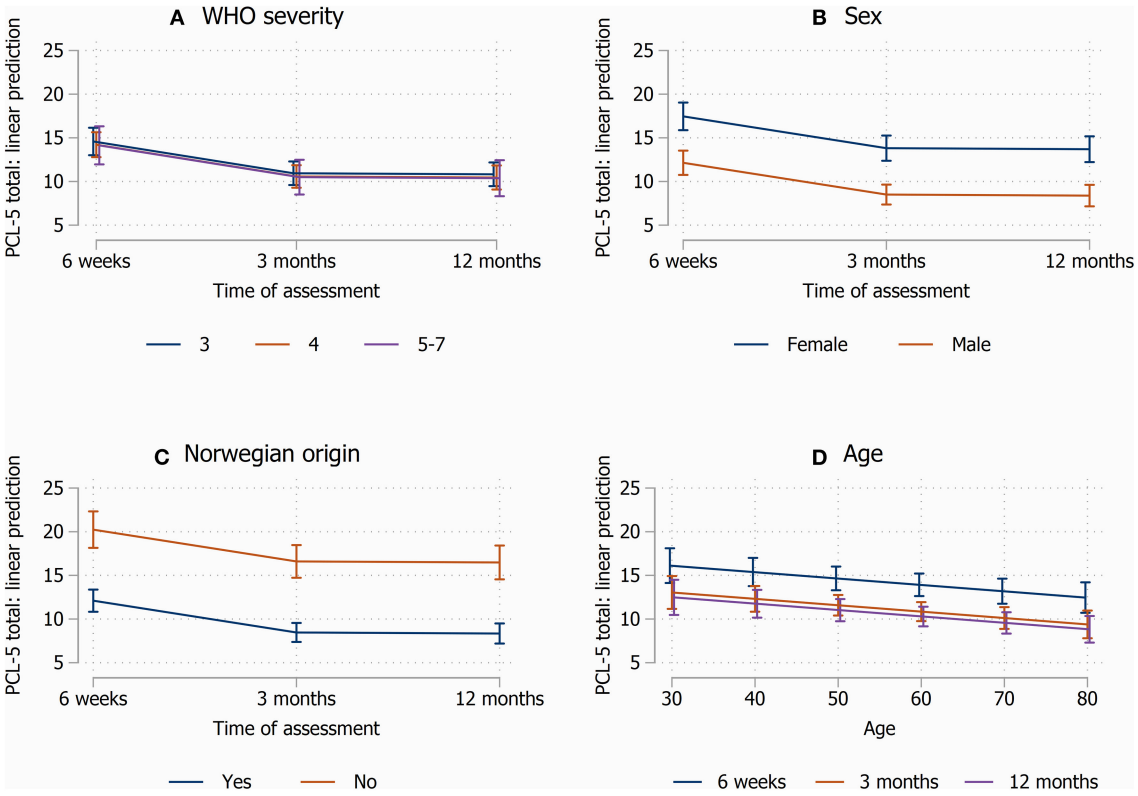

FIGURE 2
Margin plots from the linear mixed models, illutrating the effects of covariates on estimated PCL-5 scores over time. **(A)** WHO ordinal disease severity, **(B)** sex, **(C)** Norwegian origin, and **(D)** age. Other covariates than those shown were kept at mean values.

to 3.29) for WHO severity rating 4 and 1.01 (0.19 to 5.38) for severity 5–7 compared to severity 3, respectively. ICC was 0.745.

Discussion

This study has shown a prevalence of PTSD of 14% at 1.5 months, declining to 8–9% after 3–12 months. Furthermore, there was no association between the severity of acute COVID-19 and PTSD symptoms or prevalence at follow-up.

The prevalence of PTSD in this study was in line with studies with similar populations 2–12 months after hospitalization for COVID-19 (10, 11, 13–17), but lower than in some populations with more severe disease (8, 12, 18, 25). However, rates of PTSD disorders following COVID-19 as low as 3.8% has been reported in combined hospitalized/non-hospitalized samples (26).

The differences in prevalence of PTSD between our study and some other studies may possibly be explained by the use of different assessment methods, or populations.

The present study recruited a large proportion of all hospitalized patients in strict geographical catchment areas and may therefore be less affected by selection bias, e.g., healthy non-participant bias in studies recruiting based on lasting symptoms. This, and some other studies (11, 13, 15–17), may therefore be more representative of all hospitalized patients.

Symptoms of PTSD improved from 1.5 to 3 months, in line with reports from some studies from 1 to 2, or 1 to 3 months (17, 27–29), but not in others (30). There is less information on change in PTSD symptoms over as long as 12 months. One study reported the presence of moderate PTSD symptoms in 12% and severe in 6.5% 12 months after hospitalization, and these rates were unchanged from 4 months after hospitalization (16), as from 3 to 12 months in the present study. In contrast, studies have reported an increase in PTSD symptoms scores from 3 to 6 months after hospitalization (31), or from baseline to follow-up after 24–60 weeks in subjects recruited from advertisements or referrals in the community (32). Recently Mazza et al. reported a reduction in PTSD symptoms over time from 1 month to 12 months, although the change from 6 to 12 months seemed to be small (18).

In the present study we found no significant association between the severity of COVID-19 during hospitalization, i.e., graded requirement for oxygen treatment, and the total score of PCL-5 during the follow-up. This, however, supports previous

reports of no association between disease severity and adverse mental outcomes in COVID-19 (20).

In contrast, female sex was associated with higher symptom score, in line with findings in other studies (20) and PTSD in general (33). It is possible that young people are less prepared for being affected by acute severe illness (34), and that birth place outside Norway may be related to higher probability of previous PTSD, lower confidence in authorities or information given, or language difficulties.

A Charlson comorbidity index of 1, but not of $\geq$ 2, was associated with PCL-5 scores, which was most marked in the analysis in males. We do not have a good explanation for this. It could be by chance, content of the medical records, or coding issues. Some of the comorbidities might also be more important in this context, than what is reflected in the weights in this index. In the stratified analysis, this inconsistency was present only among men, who constituted 57% of the sample, and an even larger percentage of those with severe disease requiring ICU admission. In the stratified analyses, the statistical power was smaller, in particular among women, which limits conclusions to be made.

Strengths of the study are the prospective design with multiple assessments, inclusion of several large centers covering approximately 50% of the Norwegian population, and the long follow-up. The use of questionnaires and symptom-defined PTSD, instead of diagnostic interviews for assessment of PTSD represents a limitation, as in most other studies. The response rate among participants was not optimal, and may have caused a bias, and the number of patients with severe disease was small, reducing the statistical power. We did not register whether PTSD was present prior to COVID-19. However, the PCL-5 items were specifically linked to the infectious disease.

In this study the prevalence of PTSD was low. There was an early improvement in symptoms of PTSD, but no further improvement beyond 3 months. In general, about half of PTSD cases remit within 6 months, and the probability of remission does not vary much across exposure types (35). A similar remission rate of PTSD symptoms over a much shorter time period in our study suggests that COVID-19 PTSD may have a better prognosis than PTSD from most other causes.

In conclusion, the symptom load of PTSD declined from 1.5 to 3 months, with no further decline from 3 to 12 months. Symptoms of PTSD were not associated with COVID-19 severity.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Regional Committee for Medical and Health Research Ethics, Health Region South East. The patients/participants provided their written informed consent to participate in this study.

Author contributions

GE and KS conceived and designed the study, with assistance from TD and TH. EB, TL, MD, KL, and BA contributed to data collection. KS, GE, and TH conducted data analysis. KS, GE, TH, and TD contributed to interpretation of the data. KS, GE, TD, TH, EB, TL, MD, KL, and BA critically reviewed and commented on the paper. All authors approved the final version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.931349/full#supplementary-material

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The association of COVID-19 vaccine availability with mental health among adults in the United States

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Objective: To assess whether COVID-19 vaccine approval and availability was associated with reduction in the prevalence of depression and anxiety among adults in the United States.

Methods: We adopted cross sectional and quasi-experimental design with mental health measurements before vaccine availability (June 2020, $N = 68{,}009$) and after vaccine availability (March 2021, $N = 63{,}932$) using data from Census Pulse Survey. Depression and anxiety were derived from PHQ-2 and GAD-2 questionnaires. We compared rates of depression and anxiety between June 2020 and March 2021. Unadjusted and adjusted analysis with replicate weights were conducted.

Results: Depression prevalence was 25.0% in June 2020 and 24.6% in March 2021; anxiety prevalence was 31.7% in June 2020 and 30.0% in March 2021 in the sample. In adjusted analysis, there were no significant differences in likelihood of depression and anxiety between June 2020 and March 2021.

Conclusion: Depression and anxiety were not significantly different between June 2020 and March 2021, which suggests that the pandemic effect continues to persist even with widespread availability of vaccines.

KEYWORDS

COVID-19, depression, anxiety, Census pulse survey, vaccine availability

Introduction

The year 2020 brought unprecedented situations around the globe. During the COVID-19 pandemic, many households faced isolation, fear, violence, drug abuse, and anxiety. The pandemic has impacted every aspect of society resulting in economic uncertainty, limited interpersonal connections, mortality, drug abuse, and social disruption. Furthermore, America has faced riots, protests, police brutality, and political divisiveness as well (1). In April 2020, the Bureau of Labor Statistics (2020) reported a

record-high unemployment rate of 14.7% (2). As of June, 2022, more than one million deaths have been reported due to COVID-19 in the US (3).

Numerous studies in the literature have examined the impact of the COVID-19 pandemic on mental health. Two meta-analyses found that prevalence rates of depression and anxiety increased substantially during the COVID-19 outbreak (4, 5). One of them covered 12 studies with sample sizes ranging from 600 to 7,236 participants, and the pooled prevalence of depression was 25% during the COVID-19 outbreak, which is 7 times higher than the global estimated prevalence of depression of 3.44% in 2017 (4). The other meta-analysis paper covering 14 studies on the prevalence of depression with a sample size of 44,531 people, found an even higher prevalence rate of depression at 33.7% during COVID-19 (5). That study also examined prevalence of anxiety using 17 studies with a sample size of 63,439 and estimated the prevalence rate of anxiety to be also very high at 31.9% during COVID-19 (5).

Several studies have further researched the relationship between mental health during the pandemic and multiple factors such as government role, food insufficiency, housing, and income level (6–8). However, few studies considered the impact of vaccine availability and whether it helps reduce mental stress. One study on chronic kidney disease patients found that COVID-19 vaccination improved anxiety and depression in this special group of patients (9). However, there is significant skepticism about COVID-19 vaccine and it is unknown whether the availability of vaccine improved mental health in the general public.

This study aims to fill the knowledge gap by assessing if COVID-19 vaccine availability was associated with reduction in the prevalence of depression and anxiety among a nationally representative group of adults in the US. We compared the prevalence of depression and anxiety before and after COVID-19 vaccine became available using a nationally representative household survey.

Methods

Data source

The data source we used for this study is the Census pulse survey. The Census pulse survey is a nationally representative household survey was designed by the United States Census Bureau in collaboration with numerous federal agencies to measure social and economic impact due to the coronavirus pandemic in the US (10). The pulse survey contains information on demographic characteristics, education, income, employment, food sufficiency, access to healthcare physical and mental health and other COVID-19 related information such as vaccine and testing.

Study design

We adopted a cross sectional and quasi-experimental design with mental health measurements in June 2020 and March 2021. Specifically, we used the survey results from Census Household Pulse Survey (HPS) during the following two waves: Week 7: June 11- June 16, 2020, and Week 27: March 17- 29, 2021. We chose these two waves of data for comparison purposes because in June 2020 individuals were subject to high stress due to prolonged health regulations, lock downs, and social isolation due to physical and social distancing, and in March 2021 vaccines were approved and became available to all adults over 18 years of age.

The inclusion criteria for the study were non-missing data on PHQ-2 and GAD-2 scores. Between week 7 and week 27, the census pulse survey consisted of 131,941 adults representing 209,245,170 adults in the United States.

Measures

The dependent variables examined in this study were depression (yes/no) and anxiety (yes/no) based on Patient Health Questionnaire (PHQ-2) and Generalized Anxiety Disorder (GAD-2) questionnaires. PHQ-2, a patient-reported outcome measure (PROM) assesses depression symptoms with two questions. 1. Little interest or pleasure in doing things. 2. Feeling down, depressed, or hopeless. GAD-2 assesses anxiety symptoms with two questions. 1. Feeling nervous, anxious or on edge. 2. Not being able to stop or control worrying. Each question is rated from 0 to 3 (Not at all (0), several days (1), More than half the days(2), and nearly every day (3). Thus, both PHQ-2 and GAD-2 scores range from 0 to 6. Adults with PHQ-2 score 3 or greater should be screened for major depressive disorder (11). Sensitivity of PHQ-2 is 97% and specificity is 67%. Adults with GAD-2 score 3 or greater should be screened for generalized anxiety disorder (12). Sensitivity of GAD-2 is 86% and specificity is 83%. In our study, adults who scored 3 or greater PHQ-2 were classified as having depression and adults who scored 3 or more in GAD-2 were classified as having anxiety.

Other explanatory variables included age, sex, food insecurity, education, income, race and ethnicity, marital status, loss of employment (whether reported lost work during the past 4 weeks), region.

Statistical analysis

We tested group differences using Rao-Scott chi-square. Multivariable logistic regressions were used to analyze factors associated with the presence of depression and anxiety respectively. In these regressions, our main focus was on time

TABLE 1 Description of selected characteristics of adult (18 years or older) respondents in weeks 7 (june 2020) and 27 (march 2021) United States Census Pulse Survey.

		June 2020		March 2021		Chi-square	*p*-value
		N	Wt. %	N	Wt. %		
ALL		**68,009**	**100.0**	**63,932**	**100.0**		
Sex						0.085	0.770
	Female	40,588	51.6	37,828	52.0		
	Male	27,421	48.4	26,104	48.0		
Race and ethnicity						1.673	0.796
	White	52,049	63.5	48,968	65.4		
	African American	5,009	11.0	4,225	10.3		
	Latino/Hispanic	5,677	16.5	5,660	15.8		
	Asian	2,940	5.0	2,990	5.1		
	Other race	2,334	4.0	2,089	3.5		
Marital status						1.101	0.894
	Married	39,596	55.9	38,090	56.7		
	Widow	3,510	3.9	3,893	4.5		
	Sep/Div	11,859	13.9	10,937	13.7		
	Never married	12,813	26.0	10,634	24.6		
Education						1.929	0.587
	Less than high school	1,259	8.1	1,180	7.6		
	High School	21,806	51.7	19,983	49.3		
	Associate degree	6,961	8.9	6,638	10.0		
	College	37,983	31.3	36,131	33.1		
Income						14.451	0.071
	LT $25,000	6854	15.5	5645	12.7		
	$25,000–$34,999	5820	11.3	4894	9.7		
	$35,000–$49,999	7094	11.8	6297	10.8		
	$50,000–$74,999	11437	17.0	10433	16.5		
	$75,000–$99,999	9276	12.1	8462	11.7		
	$100,000–$149,999	11608	13.9	10996	14.0		
	$150,000–$199,999	5455	6.0	5452	6.4		
	GE $200,000	6319	6.3	6414	7.3		
Region						0.152	0.985
	Northeast	11,453	17.2	10,054	17.2		
	South	23,280	38.1	19,855	37.7		
	Midwest	14,141	20.4	13,172	20.7		
	West	19,135	24.2	20,851	24.3		
Employment						2.607	0.272
	Employed	38,862	54.7	37,135	59.1		
	Not employed	29,082	45.2	26,715	40.7		
Health insurance						1.266	0.737
	Private	52,992	71.0	49,944	73.2		
	Public	9,939	16.6	10,035	15.7		
	None	3,995	10.3	2,918	8.6		

(Continued)

TABLE 1 Continued

		June 2020		March 2021		Chi-square	*p*-value
		N	Wt. %	N	Wt. %		
Lost work						2.489	0.288
	Yes	26,204	47.5	22,539	43.8		
	No	41,711	52.4	41,284	56.1		
Food sufficiency						10.829	0.004
	Yes	46,016	58.4	48,773	67.9		
	No	21,803	41.2	15,020	31.8		

Based on adults (aged 18 or older) who responded to the United States Census Pulse Survey in week 7 or Week 27, with no missing data in Patient Health Questionnaire-2 and Generalized Anxiety Disorder 2-item questions. Due to missing data (marital status, employment, income, health insurance, lost work, food sufficiency), the column percentages may not add to 100%. Missing data are not included in the table. Group differences were tested with Rao-Scott chi-square statistics.
LT, Less than; GE, Greater than or equal; Sep/Div, Separated Divorced; Wt, Weighted. The red indicates that these are statistically significant.

and we controlled for age, sex, food insecurity, education, income, race and ethnicity, marital status, loss of employment, and region. All analyses were conducted with the SAS survey procedures to take the survey weights provided by the Census pulse survey into consideration.

Results

Table 1 illustrates the characteristics of adult respondents in week 7 and week 27 in US Census Pulse Survey. There were 51.8% females, 64.3% white, 10.7% African American, 16.2% Hispanic/Latino, 5.0% Asian and 3.8% other race or multiracial; and 9.6% did not have health insurance. Demographic, socio-economic, and healthcare access (age, sex, race and ethnicity, education, and health insurance) did not differ between June 2020 and March 2021 (Table 1).

With respect to depression, 25.0% in June 2020 and 24.6% in March 2021 had PHQ-2 score ≥ 3 (Table 2). With respect to anxiety, 31.7% in June 2020 and 30.0% in March 2021 had a GAD-2 score ≥ to 3 (Table 2). The differences were not statistically significant. In adjusted analysis, there were no significant differences in likelihood of depression and anxiety between June 2020 and March 2021.

In adjusted logistic regression (Table 3), those who reported food insufficiency (AOR = 2.93, 95% CI = 2.25, 3.79) and those who were never married (AOR = 1.52, 95% CI = 1.02, 2.28) were more likely to have depression compared to those who reported food sufficiency and were married. Adults who did not lose work during the pandemic were less likely to have depression (AOR = 0.62, 95% CI = 0.47, 0.83) compared to those who lost employment.

In adjusted logistic regression (Table 3), those who reported food insufficiency (AOR = 2.82, 95% CI = 2.09, 3.81), loss of employment (AOR = 0.57, 95% CI = 0.44, 0.74) were more likely to be anxious compared to those with food sufficiency and did not lose employment. Being married was associated with lower odds of anxiety (AOR = 1.25, 95% CI = 0.85, 1.83). Being a female was associated with higher odds of anxiety (AOR = 1.39, 95% CI = 1.06, 1.83) compared to males.

Discussion

This study examined the association of COVID-19 vaccine availability and mental health. We observed adult depression prevalence rate at 25.0% in June 2020 and at 24.6% in March 2021 based on Census pulse survey. Therefore, the result suggests that the depression prevalence was relatively stable over this time period. We also report that anxiety was initially 31.7% at the beginning of the pandemic and 30.0% in March 2021. People who lost their jobs, had food insecurity, and were older were more likely to experience depression and anxiety in the study period. Females, in general, were more likely to experience anxiety, and people who were never married were more likely to experience depression during the study period.

These depression and anxiety rates were much higher than numbers found in the literature in the year preceding the COVID-19 pandemic. For example, one study found that in 2019, 18.5% of U.S. adults were experiencing depression, of which 11.5% reported mild symptoms, 4.2% reported moderate symptoms, and 2.8% reported severe symptoms (13). Another study showed that during that same year, there were 15.6% who reported experiencing the anxiety, of which 9.5% reported mild symptoms, 3.4% reported moderate symptoms, and 2.7% reported severe symptoms (14).

Several studies during the pandemic showed an increase in depression and anxiety symptoms that were above the 2019 levels and were similar to the results of this study. A meta-analysis with pooled prevalence showed depression levels at 25% from January 1, 2020 to May 8, 2020 (4). In another meta-analysis conducted without a lower time limit and until May 2020, the prevalence of depression was 33.7% (much higher than our results); however, the prevalence of anxiety was 33.7% (similar to our results) (5). Other researchers have also reported that there was a higher burden of depression symptoms among

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TABLE 2 Description of selected characteristics of adult respondents by depression and anxiety (row percentages) United States Census Pulse Survey–week 7 (june 2020) and week 27 (march 2021).

		With depression				With anxiety			
		N	Wt. %	Chi-square	*p*-value	N	Wt. %	Chi-square	*p*-value
ALL	**26,903**	**24.8**			**36,484**	**30.9**			
Time				0.035	0.852			0.48	0.489
	June 2020	14,285	25.0			20,221	31.7		
	March 2021	12,618	24.6			16,263	30.0		
Sex				1.666	0.197			7.119	0.008
	Female	17,240	26.3			24,376	34.3		
	Male	9663	23.2			12,108	27.3		
Race and ethnicity				3.900	0.420			2.812	0.590
	White	19,229	23.2			26,662	29.6		
	African American	2,290	27.6			2,969	34.2		
	Latino/Hispanic	2,946	28.3			3,840	34.1		
	Asian	1,101	22.6			1,369	26.6		
	Other race	1,337	33.3			1,644	36.6		
Marital status				35.555	<0.001			25.033	<0.001
	Married	12,003	18.6			18,150	25.3		
	Widow	1,459	24.8			1,668	26.4		
	Sep/Divorced	6,105	30.2			7,584	35.8		
	Never married	7,203	35.8			8,915	41.4		
Education				12.739	0.005			6.895	0.075
	LT High School	835	31.8			966	37.7		
	High School	10,881	27.7			13,257	32.5		
	Associate degree	3,180	26.8			4,073	33.5		
	College	12,007	18.0			18,188	26.0		
Income				36.893	<0.001			34.120	<0.001
	LT $25,000	4,741	37.3			5,470	43.0		
	$25,000–$34,999	3,170	32.0			3,868	37.3		
	$35,000–$49,999	3,384	29.2			4,220	34.8		
	$50,000–$74,999	4,723	24.6			6,343	31.4		
	$75,000–$99,999	3,141	20.7			4,461	26.7		
	$100,000–$149,999	3,271	16.9			5,006	22.6		
	$150,000–$199,999	1,353	14.6			2,249	21.3		
	GE $200,000	1,353	13.2			2,388	19.6		
Region				0.833	0.842			0.880	0.830
	Northeast	4,149	23.5			5,945	28.1		
	South	9,218	25.8			12,230	35.1		
	Mid-west	5,178	23.4			7,053	43.5		
	West	8,358	25.5			11,256	37.4		
Employment				6.291	0.043			1.974	0.378
	Employed	14,169	21.9			20,931	41.0		
	Not employed	12,702	28.6			15,512	22.4		
Health insurance				16.766	<0.001			13.160	0.004
	Private	18,742	21.9			26,569	20.9		
	Public	5,113	29.9			6,182	48.1		
	None	2,531	37.8			3,041	25.9		

(Continued)

TABLE 2 Continued

		With depression				With anxiety			
		N	Wt. %	Chi-square	*p*-value	N	Wt. %	Chi-square	*p*-value
Lost work				45.427	<0.001			61.924	<0.001
	Lost work	14,147	33.2			18,832	41.0		
	No	12,715	17.8			17,594	22.4		
Food sufficiency				133.962	<0.001			89.638	<0.001
	Yes	12,523	15.4			18,803	20.9		
	No	14,309	40.9			17,592	48.1		
Comorbid dep and anxiety				496.000	<0.001			496.000	<0.001
	Yes	21610	65.7			21610	81.8		
	No	5293	6.5			14874	14.1		

Based on adults (aged 18 or older) who responded to the United States Census Pulse Survey in week 7 or Week 27, with no missing data in Patient Health Questionnaire-2 and Generalized Anxiety Disorder 2-item questions. Missing data (marital status, employment, income, health insurance, lost work, and food sufficiency) are not presented in the table. Group differences were tested with Rao-Scott chi-square statistics.

Dep, Depression; LT, Less than; GE, Greater than or equal; Sep/Div, Separated Divorced; Wt, Weighted. The red indicates that these are statistically significant.

U.S. adults in a study from March 31, 2020, to April 13, 2020 in which 27.8% reported depression symptoms (15).

Our study differs from the previous ones in that its time frame encompasses the availability of the COVID-19 vaccine for the general public and the potential for some resolution of depression and anxiety. The initial high levels of depression and anxiety were not unexpected as COVID-19 brought uncertainty and stress with its high transmission and number of hospitalizations and deaths in the early months of 2020. Additionally, the poor health messaging, lockdowns, economic downturn, and poor management of the pandemic in early 2020 were also factors that could be expected to impact depression and anxiety symptoms. A prior study found that COVID-19 vaccination improved anxiety and depression in chronic kidney disease patients (9). However, in this study, depression and anxiety levels remained high in March 2021, despite the widespread availability of the vaccines that were shown to sharply decrease severe COVID-19, hospitalizations, and death (16).

Three main factors may explain the high levels of depression and anxiety that did not subside after the availability of vaccines: vaccine hesitancy, concern for children ineligible for the vaccine, and social determinants. There is significant vaccine hesitancy in the Us. One online survey indicated that 41% of participants reported a belief of an adverse effect on fertility with the vaccination, and 38% reported being unsure about an adverse effect on fertility (17). In the U.S., the mixed messages, political discourse, and social media were evident. In a study of social networking tweets, the most retweeted tweets had misinformation (18). The researchers suggested that many of the tweets were from anti-vaxxer activists and systematic professional sources (18). Prior studies that shown that individuals with less education, less income, and who were black were more likely to have vaccine hesitancy or decline vaccinations (19, 20). Another study found that children and adolescents in England who had prior COVID-19 infection were more hesitant to receive vaccine and also had lower level of depression and anxiety (21). It is interesting to note that in a study conducted in Germany, COVID-19-related anxiety was associated with higher vaccine acceptance (22).

The other potential factor for maintaining high levels of anxiety and depression symptoms was concern about children and COVID-19. In March 2021, children under 12 years did not have access to vaccinations, and school boards were considering returning the children to in-person learning. In a study conducted in mid-March 2020, parents of children from primary school to college were surveyed, and parents who perceived stress and had children in middle or high school were at greater risk for depression and anxiety (23).

Our findings also indicated an association of depression and anxiety with social determinants of health such as employment, food sufficiency, and marital status (a proxy for social support). Regardless of COVID-19, individuals with untreated depressive disorders had lower employment rates (24). In a study of 424 adults, employment at baseline was associated with lower depressive symptoms throughout the life course of the depression (25). In one study, from June 15 to June 30, 2020, direct or household employment loss (job insecurity) was associated with a greater risk of poor mental health (26). Food insecurity has also been an identified risk factor for depression in older adults (27, 28). Researchers conducting a meta-analysis for risk factors for depression and anxiety indicated a positive relationship with food insecurity (29).

In our study, we found that persons who had never married were associated with depressive symptoms. In a literature review of marriage and psychiatric illness prior to the pandemic, marriage was both a protecting and predisposing factor for psychiatric illness, depending upon the quality of the marriage

TABLE 3 Adjusted odds ratios and 95% (confidence intervals) selected characteristics from separate logistic regressions on depression and anxiety United States Census Pulse Survey–Week 7 (june 2020) and week 27 (march 2021).

		AOR	95% CI	*p*-value	AOR	95% CI	*p*-value
Time							
	June 2020(Ref)						
	March 2021	0.87	[0.65,1.16]	0.3495	0.94	[0.73, 1.20]	0.6060
Sex							
	Female	1.14	[0.85, 1.53]	0.3690	1.39	[1.06, 1.83]	0.0172
	Male (Ref)						
Age	0.93	[0.89, 0.97]	0.0005	0.91	[0.88, 0.95]	<0.001	
Race and ethnicity							
	White (Ref)						
	AA	0.82	[0.50, 1.34]	0.4221	0.82	[0.50, 1.33]	0.4174
	Latino	0.74	[0.43, 1.26]	0.2629	0.70	[0.43, 1.13]	0.1408
	Asian	0.85	[0.40, 1.79]	0.6615	0.70	[0.37, 1.33]	0.2677
	Other race	1.11	[0.58, 2.14]	0.7424	0.91	[0.45, 1.83]	0.7844
Marital status							
	Married (Ref)						
	Widow	1.55	[0.78, 3.11]	0.2104	1.15	[0.56, 2.37]	0.6979
	Sep/Div	1.45	[1.00, 2.12]	0.0506	1.28	[0.88, 1.85]	0.1922
	Never Married	1.52	[1.02, 2.28]	0.0381	1.25	[0.85, 1.83]	0.2455
Education							
	LT HS	1.18	[0.55, 2.54]	0.6628	0.99	[0.52, 1.89]	0.9794
	HS	1.18	[0.86, 1.62]	0.3047	0.94	[0.72, 1.24]	0.6712
	Assoc deg	1.24	[0.75, 2.04]	0.4065	1.06	[0.69, 1.63]	0.7816
	College (Ref)						
Income							
	LT $25,000 (Ref)						
	$25,000–$34,999	0.98	[0.53, 1.81]	0.9355	0.95	[0.56, 1.62]	0.8593
	$35,000–$49,999	0.98	[0.58, 1.65]	0.9282	0.96	[0.53, 1.73]	0.8897
	$50,000–$74,999	0.87	[0.51, 1.49]	0.6096	0.90	[0.54, 1.51]	0.6906
	$75,000–$99,999	0.83	[0.44, 1.56]	0.5547	0.82	[0.47, 1.43]	0.4821
	$100,000–$149,999	0.76	[0.40, 1.45]	0.3986	0.74	[0.41, 1.31]	0.2970
	$150,000–$199,999	0.72	[0.36, 1.45]	0.3566	0.75	[0.40, 1.42]	0.3764
	GE $200,000	0.72	[0.35, 1.49]	0.3738	0.75	[0.38, 1.47]	0.3981
Region							
	Northeast (Ref)						
	South	1.06	[0.71, 1.57]	0.7806	1.05	[0.72, 1.53]	0.8087
	Mid-west	0.96	[0.60, 1.53]	0.8623	0.93	[0.60, 1.44]	0.7473
	West	1.04	[0.68, 1.61]	0.8491	1.07	[0.70, 1.62]	0.7625
Health insurance							
	Private (Ref)						
	Public	1.12	[0.77, 1.63]	0.5606	1.08	[0.73, 1.59]	0.6935
	None	1.14	[0.70, 1.88]	0.5965	1.10	[0.65, 1.85]	0.7215
Lost work							
	Lost work (Ref)						
	No	0.62	[0.47, 0.83]	0.0012	0.57	[0.44, 0.74]	<0.001
Food sufficiency							
	Yes (Ref)						
	No	2.92	[2.25, 3.79]	0.0000	2.82	[2.09, 3.81]	<0.001

Based on adults (aged 18 or older) who responded to the United States Census Pulse Survey in week 7 or Week 27, with no missing data in Patient Health Questionnaire-2 and Generalized Anxiety Disorder 2-item questions.

AOR, Adjusted Odds Ratio; 95% CI, 95% Confidence Interval; Dep, Depression; LT, Less than; GE, Greater than or equal; Sep/Div, Separated Divorced.

(30). A study of job loss during the pandemic and marriage indicated that married individuals were 1–2% less likely to develop mental health problems related to work/income (31). Another study indicated that during the pandemic, the quality of the marriage was related to depression and anxiety and that individuals with no relationships scored better than individuals with poor ones (32).

Our finding that depression and anxiety symptoms did not improve after COVID-19 vaccine became available has implications for future mental healthcare needs and healthcare delivery. During the period studied in this research, there was increased use of telehealth for anxiety and depression in some settings (33). In one study, telehealth reduced depression but not anxiety during the pandemic (34). In a survey study conducted in Arkansas, 42% of participants reported using telehealth; and those with anxiety and/or depression had three times greater odds than those with no diagnosis (35). Telehealth may be a viable means by which to meet mental healthcare needs beyond COVID-19.

With each wave of COVID-19, there may continue to be high levels of depression and anxiety symptoms. The means to provide pharmacological and non-pharmacological therapies to alleviate the mental health burden need to be expanded. Future studies need to explore barriers to COVID-19 related mental healthcare utilization and the impact of mental health therapies on outcomes among adults with depression and or anxiety.

Strengths and limitations

Our study has many strengths and some limitations. We used nationally representative data with near real-time collection. The findings from this study may inform public health planning and policies to address mental health. Availability of repeated cross-sections enabled assessment of COVID-19 related mental health burden over time. However, the survey lacked information on some variables such as chronic conditions, health status, loss/impact of COVID-19 on family and friends, the severity of depression and anxiety, physical activity, and vaccine hesitancy that may have influenced mental health.

Conclusion

Depression and anxiety symptoms did not change significantly between June 2020 and March 2021. These results suggest that the effects of the pandemic on mental health continue to persist despite the widespread availability of vaccines that would have been considered to assuage some of the symptoms.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.census.gov/programs-surveys/household-pulse-survey/datasets.html.

Author contributions

CS and US contributed to conception and design of the study. LR and US performed the statistical analysis. All authors contributed to the writing of the manuscript, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Increased anxiety from fear of Omicron in China as compared to North America and Western Europe: A cross-sectional Kendall's tau-b analysis using the generalized anxiety disorder 7-item questionnaire

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Background: Policies dealing with the Coronavirus Disease 2019 (COVID-19) pandemic vary across the globe, the different governmental responses then affect the public perception of COVID-19. Many unofficial Chinese media outlets frequently spread misinformation about COVID-19 and exaggerated reports of rare sequelae of Omicron for monetization and attention seeking, leading to panics in the Chinese public. In comparison the attitudes toward Omicron in other countries around the world, especially in North America and Western Europe have shifted to a more relaxed stance.

Objective: This article primarily aims to investigate the association between Chinese people's attitudes toward the potential after-effects of Omicron and their anxiety status, as compared to these of people living in North America or Western Europe.

Methods: We conducted a questionnaire survey *via* the Credamo and collected valid data from 500 Chinese (not living in Shanghai), another 500 Chinese (living in Shanghai) and 500 people living in North America or Western Europe in June 2022. Kendall's coefficient of rank correlation tau-sub-b was used to examine this association.

Results: The results suggested that subjective attitudes of Chinese participants toward the sequelae of Omicron were positively and significantly associated with their anxiety status [i.e., the Generalized Anxiety Disorder 7-item (GAD-7) scores] in Shanghai (China) (Tb = 0.44, $p < 0.01$) and other parts of China outside Shanghai (Tb = 0.37, $p < 0.01$). However, no such significant correlation was found in North America & Western Europe (Tb = -0.01, $p > 0.05$).

Conclusion: Our findings showed that Chinese participants who were more worried about the after-effects of Omicron had higher levels of anxiety. Although it is true that Long COVID-19 should be a concern, exaggerated media reporting can impact negatively on an individual's mental wellbeing. Only through the dissemination of robust scientific studies, the misinformation and the fears that follow it can be put to rest.

KEYWORDS

anxiety, COVID-19, Omicron, pandemic, sequelae

Introduction

Background

Coronavirus Disease 2019 (COVID-19) outbreak elicited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in December 2019 (1). As of June 7, 2022, the COVID-19 has led to more than 536 million confirmed cases and 6.32 million deaths globally (2). It has been considered a serious event, impacting significantly on the mental health of the global population (3).

Coronavirus disease 2019 and anxiety

In order to reduce the risk of coronavirus exposure in public, staying-at-home campaign was highly recommended or even mandated (4). As a result, the fear of contracting the virus, high unemployment due to economic loss, interrupted daily routine during recurrent periods of lockdown, the inability of engaging in most canceled outdoor events and other factors induced by COVID-19 severely impacted public mental health (5). In the general Chinese population, varying degrees of anxiety resulted from many factors, such as overestimating threat and intolerance of uncertainty to COVID-19, ranging from 2 to 37%, yielded a pooled prevalence of 19.1% (6–14). In North America and Western Europe, a pooled prevalence of anxiety was slightly lower than 15% (15).

Omicron and after-effects

Omicron, a newest and most popular variant of the Coronavirus, firstly discovered on November 24, 2021, has clinical characteristics mainly consisting of mild symptoms but extremely high communicable capacity (16). With reference to the after-effects of COVID-19, previous studies showed that delta variant or other preceding variants could possibly cause patients many impacts such as hair loss, altered sense of smell and taste (17–19), while the consequence of Omicron is unclear and still under evaluation (20).

Omicron in China

The COVID-19 pandemic was well controlled in China owing to its zero-tolerance approach to coronavirus applied in the past 2 years (21–24), but for this reason, no herd immunity barrier has been established (25); meanwhile, other countries (especially Western countries) attempted coexistence with COVID-19 in order to return things that were severely impacted such as economy by pandemic to normal (26). Hence, once the pandemic spread internationally, the potential risk caused by highly contagious Omicron to the whole country (i.e., China) could be very high (27). Unfortunately, Omicron suddenly broke out in Shanghai, China starting in March and continued to grow at a rate of about 10,000 confirmed patients per day until May (28, 29). The dire situation was not brought under control until early June (30, 31).

People's perception of coronavirus disease 2019 *via* media outlets in China and the West

It is important to note that all traditional news media outlets in China are controlled by Central Publicity Department (CPD) the information published come under more censorship than their western counterparts (32). As is often the case, alternative forms of traditional media flourished instead under the radar of the government control regime, citizen journalism as it is coined became the new way many people obtain news (33, 34). From this understanding it is evident that the flourishing unofficial Chinese media outlets, mostly owned by individuals and private companies, are comparable with traditional news media in the West in terms of function. The popular hosting platforms (e.g., WeChat, Sina Microblog, ZhiHu, and Bilibili)

for the unofficial Chinese media outlets are also in and of itself a social media platform, making it very easy to share articles and comments to friends and families. Similar to how western traditional media also uses social media (e.g., Twitter and Facebook) to promote their news articles for views. Therefore, from this perspective, the comparison of how media affects individuals' perception of events is valid in this context, though exceptions that disputable opinions or comments are restricted to access may still exist in these Chinese media outlets.

However, compared to North America and Western Europe, where more than half of the residents there have had actual experience with COVID-19 (35, 36), the low COVID-19 prevalence in China led to a greater likelihood that Chinese people obtain the information of COVID-19 through the media outlets (37, 38). Hence, Chinese people's perception toward COVID-19 could be, to a much larger extent, dependent on unofficial reports of these media outlets, which have been found an effective medium to acquire relevant information for the public (37–39).

The current study

Many Chinese owned media outlets frequently spread non-evidence-based information of COVID-19 or greatly exaggerated rare sequelae of Omicron lacking common consent of systematic study for the sake of attention, leading Chinese people to panic situation, in comparison with the large shift in attitudes toward Omicron in other countries around the world, especially in North America and Western Europe (40–42). Therefore, this article mainly intends to explore the association between Chinese people's attitudes toward the potential sequelae of Omicron and their anxiety levels, as compared to these of people residing in North America or Western Europe. In addition, this study is also intended to present up-to-date information regarding risks of evidence-based sequelae that Omicron may cause to patients. Based on the backgrounds of COVID-19 and its information's propagation *via* media outlets mentioned above in these countries, we propose Hypothesis 1 and Hypothesis 2.

1. Chinese people holding more negative attitudes toward the after-effects of Omicron will also have higher anxiety scores, compared to those residing in North America and Western Europe.
2. Residents in North America and Western Europe will have lower anxiety levels in terms of Generalized Anxiety Disorder 7-item (GAD-7) mean scores, compared to those residing in China.

Materials and methods

Overview

We conducted a questionnaire survey *via* the Credamo, a professional online survey platform similar to Qualtrics Online Sample (43), by randomly recruiting intending participants who were interested in our study, starting on June 1, 2022, and ending on June 8, 2022, and the use of human data from the surveys was carried out ethically in accordance with the principles of the Declaration of Helsinki (as revised in 2013). During this process, a Chinese version of questionnaire was used to collect the data from Chinese participants directly through a webpage-based answering platform on Credamo.[1] An English version of the same questionnaire was separately submitted to the Credamo company to help collect the data from North America and Western Europe. To eliminate any potential misunderstanding of participants to questions due to different versions of questionnaires (i.e., Chinese vs. English), each question in the questionnaire was followed with a relevant example explaining the intention we were hoping to ask. On the first page of the questionnaire survey all participants received an adequate description of the purpose of the survey and were asked to tick a box to confirm an online informed consent prior to filling out survey. Furthermore, all data were collected anonymously through the Credamo using continuous identifier numbers to distinguish participants instead of recording their names or other sensitive information.

For survey answering quality, two attention check questions at different point in the survey were used. A one US dollar or RMB/GBP/Euro equivalent monetary incentive was offered for each participant who completed the survey. Meanwhile, we manually checked the time taken for completing each survey as well as the IP address of responders in case of the same responders joining the survey multiple times. Moreover, on the first page of the questionnaire survey, participants were informed about finishing the questionnaire truthfully under personal anxiety status developed explicitly during the pandemic era that Omicron dominated. Also, they were strictly informed that only those who did not experience any personal COVID-19 related situation that had caused their mental status deteriorated severely, were permitted to complete the questionnaire survey.

Questionnaire contents

The questionnaire was mainly comprised of the following information collected:

1 www.credamo.com

1. Demographic information
2. How many shots of vaccine did you get?
3. Have you ever been infected with COVID-19?
4. Do you support coexistence or zero-tolerance approach of the Omicron-dominated pandemic in your country?
5. Do you have psychological fear toward your real-life friends who were infected with COVID-19 (i.e., do you want to be wary of them inwardly)?
6. Subjective attitudes toward Omicron about its after-effects (i.e., "to what extent do you think Omicron could cause sequelae?")
7. The 7-item Generalized Anxiety Disorder-7 (GAD-7) scale.

A total of 1,500 people were initially recruited to complete the questionnaire survey. Invalid data were excluded, and new participants were recruited until 1,500 individual data fulfilled our standard inclusion criteria. Finally, a total of 1,623 people living in China, North America or Western Europe were independently recruited and surveyed through the Credamo platform. Of them, 78 were excluded for the failure in the attention check questions (e.g., responded wrongly to the instruction "please chose the answer Blue"), 33 were excluded for completing the survey in less than 100 s, 12 were excluded with additional analyses for other reasons such as answering the questionnaire questions inconsistently or contradictorily. Eventually, a valid sample of 1,500 participants was analyzed collectively (688 females and 812 males; mean age = 26.74 years, *SD* = 3.81 years; age range: 18–34 years).

Generalized anxiety disorder 7-item scale

The anxiety status of the participants was assessed using the 7-item version of the Generalized Anxiety Disorder scale or GAD-7. It consists of seven items based on seven core symptoms, asking respondents how often they experienced these symptoms in the past 2 weeks, and is preferably used to measure an individual's proximate level of anxiety in a timely manner during the pandemic era (44–48). For each item, participants were asked to choose the degree to which they agreed or disagreed with the statement, on a scale of 0–3, with 0 denoting "not at all," 1 denoting "several days," 2 denoting "more than half the days" and 3 denoting "nearly every day." In the GAD-7 scale, total score of participants for the seven items ranging from 0 to 21 was summed up. A total score of 0–4, 5–9, 10–14, and 15–21 were classified as minimal anxiety, mild anxiety, moderate anxiety, and severe anxiety, respectively. Hence, a higher total score indicated a higher level of anxiety status of participants. In this study, the Cronbach's alpha coefficient for the total scale was 0.91, suggesting excellent overall internal consistency.

Statistical analysis

All statistical analyses were performed using the software program SPSS (version 26.0) except for the data cleaning process which included detection and removal of invalid or missing data completed on the Credamo data platform. A reliability test was conducted for the GAD-7 scale, using Cronbach's alpha coefficients as a measure of internal consistency ($\alpha > 0.70$ regarded as acceptable). Mean differences were compared by using parametric tests. Finally, Kendall's coefficient of rank correlation tau-sub-b was used to examine the association between the subjective attitudes of participants toward the after-effects of Omicron (ordinal variable) and the GAD-7 self-report scale scores (continuous variable), according to Khamis (49).

Results

Sample characteristics

There were 1,623 individuals from mainland China (Shanghai vs. non-Shanghai), North America and Western Europe, who enrolled in the survey, and 1,500 (92.4%) were included in the analysis participants after data cleaning. Relevant descriptive statistics were presented in **Table 1**.

Mean comparison of general anxiety disorder 7-item scores

Regarding the mean differences of GAD-7 shown in **Table 2**, our results suggested that no any statistically significant difference was found in terms of gender, vaccination status, infection status of participants from outside Shanghai, view of coexistence with COVID-19, psychological fear toward friends infected with COVID-19 within groups (i.e., Non-Shanghai area (China), Shanghai (China), and North America and Western Europe; all $p > 0.05$), except for subjective attitudes of participants toward the sequelae of Omicron (all $p < 0.05$). However, there was strongly significant difference with reference to the mean of GAD-7 scores by area between groups as shown in **Figure 1** (mean $\pm$ *SD* = 5.768 $\pm$ 3.59, 9.034 $\pm$ 3.93 and 3.94 $\pm$ 2.53, respectively; $F = 287.485$, $p < 0.001$).

Kendall's tau-b analysis model

In **Table 3**, Kendall's coefficient of rank correlation tau-sub-b as a type of inferential statistics was conducted to investigate the correlation between subjective attitudes of participants toward the sequelae of Omicron and their anxiety levels among different areas. Most importantly, it was found that subjective attitudes of Chinese participants toward the sequelae

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TABLE 1 Sample description.

	n (%)		
***N* = 1,500**	**China (Shanghai) *n* = 500**	**China (non-Shanghai) *n* = 500**	**North America or Europe *n* = 500**
Variables			
Gender			
Male	278 (55.6)	291 (58.2)	243 (48.6)
Female	222 (44.4)	209 (41.8)	257 (51.4)
Vaccination status			
1 dose	13 (2.6)	10 (2)	68 (13.6)
2 doses	28 (5.6)	110 (22)	105 (21.0)
3 doses	459 (91.8)	380 (76)	327 (65.4)
Infection status			
Yes	14 (2.8)	4 (0.8)	393 (78.6)
No	486 (97.2)	496 (99.2)	107 (21.4)
View of coexistence with COVID-19			
Support zero-tolerance approach (because of fearing sequelae of Omicron)	212 (42.4)	335 (67.0)	39 (7.8)
Support zero-tolerance approach (because of misgiving medical resource crowding)	93 (18.6)	79 (15.8)	20 (4)
Support co-existence with virus as much as possible	195 (39)	86 (17.2)	441 (88.2)
Psychological fear toward friends infected with COVID-19			
No	247 (49.4)	259 (51.8)	483 (96.6)
Yes	253 (50.6)	241 (48.2)	17 (3.4)
Subjective attitude toward the sequelae of Omicron			
No sequelae	5 (1.0)	11 (2.2)	283 (56.6)
Mild sequelae	54 (10.8)	229 (45.8)	106 (21.2)
Moderate sequelae	185 (37.0)	146 (29.2)	67 (13.4)
Severe sequelae	256 (51.2)	114 (22.8)	44 (8.8)

of Omicron were positively and significantly associated with their anxiety status (i.e., GAD-7 scores) in Shanghai (China) ($Tb = 0.44$, $p < 0.01$) and other parts of China outside Shanghai ($Tb = 0.37$, $p < 0.01$). However, no such significant correlation was found in North America & Western Europe ($Tb = -0.01$, $p > 0.05$). This meant that there was a tendency for Chinese participants to report higher levels of anxiety the more they feared the sequelae of Omicron.

Discussion

The given study mainly examined the association between participants' attitudes toward the potential after-effects of Omicron and their anxiety status, and mean of GAD-7 scores of participants from different areas (Shanghai vs. Outside Shanghai within China vs. North America and Western Europe). The results of our study primarily showed that the more severe the sequelae of omicron the Chinese participants perceived, the higher their anxiety levels, but such relationship did not statistically and significantly exist in participants from North America and Western Europe. Also, regarding the mean of GAD-7 scores among different areas, participants from North America and Western Europe had relatively lowest anxiety levels (mean $\pm$ SD = 3.94 $\pm$ 2.53), followed by participants from China outside Shanghai (mean $\pm$ SD = 5.768 $\pm$ 3.59), and then participants from Shanghai (mean $\pm$ SD = 9.034 $\pm$ 3.93). These findings were consistent with our primary hypotheses in the introduction section. In addition, according to the results of one-way ANOVA as shown in Table 2, no statistical and significant difference of participants' levels of anxiety was found in terms of gender, vaccination status, infection status of participants from outside Shanghai, subjective view of coexistence with COVID-19, personal psychological fear toward friends infected with COVID-19. However, there was a significant difference in terms of the infection status (Yes vs. No) of participants in Shanghai (China) and their corresponding GAD-7 mean scores. This might be understandable that the people in Shanghai were urgently required to respond a sudden pandemic situation, which led to a panic to the public with increased anxiety.

TABLE 2 General anxiety disorder 7-item (GAD-7) scores of participants (N = 1,500).

Variables	GAD-7 scores								
	Means (*SD*)			[95%CI]			*p*		
	CN SH	CN Non-SH	NA and WE	CN SH	CN Non-SH	NA and WE	CN SH	CN Non-SH	NA and WE
Gender							0.578	0.731	0.664
Male	8.74 (3.97)	5.23 (2.34)	3.77 (1.80)	[8.27, 9.21]	[4.96, 5.50]	[3.54, 4.00]			
Female	9.11 (3.75)	6.03 (2.08)	4.11 (2.66)	[8.62, 9.60]	[5.75, 6.31]	[3.78, 4.44]			
Vaccination status							0.344	0.544	0.650
1 Dose	8.69 (3.97)	7.00 (3.33)	4.21 (2.59)	[6.53, 10.85]	[4.93, 9.07]	[3.59, 4.83]			
2 Doses	10.07 (4.81)	5.70 (3.71)	3.92 (2.57)	[8.29, 11.85]	[5.01, 6.39]	[3.43, 4.41]			
3 Doses	8.98 (3.87)	5.76 (3.56)	3.89 (2.52)	[8.63, 9.33]	[5.40, 6.12]	[3.62, 4.16]			
Infection status							0.000	0.837	0.067
Yes	4.06 (2.65)	10.50 (4.04)	3.89 (2.48)	[2.67, 5.45]	[6.54, 14.46]	[3.64, 4.14]			
No	7.07 (4.11)	5.73 (3.56)	4.15 (2.74)	[6.70, 7.44]	[5.42, 6.04]	[3.63, 4.67]			
VOC							0.936	0.092	0.099
SZAFS	9.17 (3.86)	5.63 (3.54)	4.73 (3.07)	[8.62, 9.72]	[5.25, 6.01]	[3.77, 5.69]			
SZAMM	8.93 (3.93)	7.16 (4.17)	4.64 (2.29)	[8.13, 9.73]	[6.24, 8.08]	[3.64, 5.64]			
SCV	9.35 (3.31)	6.05 (3.17)	4.50 (2.87)	[8.89, 9.81]	[5.38, 6.72]	[4.23, 4.77]			
PFTF							0.823	0.526	0.284
Yes	9.13 (3.86)	5.83 (3.54)	3.29 (2.14)	[8.65, 9.61]	[5.38, 6.28]	[2.27, 4.31]			
No	8.94 (4.00)	5.71 (3.64)	3.96 (2.55)	[8.44, 9.44]	[5.27, 6.15]	[3.73, 4.19]			
SATSO							0.000	0.000	0.060
No sequelae	6.80 (5.36)	3.64 (3.91)	3.95 (2.50)	[2.11, 11.49]	[1.33, 5.95]	[3.66, 4.24]			
Mild sequelae	7.04 (3.93)	4.64 (3.36)	3.45 (2.69)	[5.99, 8.09]	[4.20, 5.08]	[2.94, 3.96]			
Moderate sequelae	7.17 (2.73)	5.31 (2.34)	4.42 (2.23)	[6.78, 7.56]	[4.93, 5.69]	[3.89, 4.95]			
Severe sequelae	10.85 (3.79)	8.82 (3.61)	4.34 (2.68)	[10.39, 11.31]	[8.16, 9.48]	[3.55, 5.13]			

CN, China, SH, Shanghai, NA, North America; WE, Western Europe; VOC, View of coexistence with COVID-19; SZAFS, Support zero-tolerance approach (because of fearing sequelae of Omicron); SZAMM, Support zero-tolerance approach (because of misgiving medical resource crowding); SCV, Support co-existence with virus as much as possible; PFTF, Psychological fear toward friends infected with COVID-19; SATSO, Subjective attitude toward the sequelae of Omicron.

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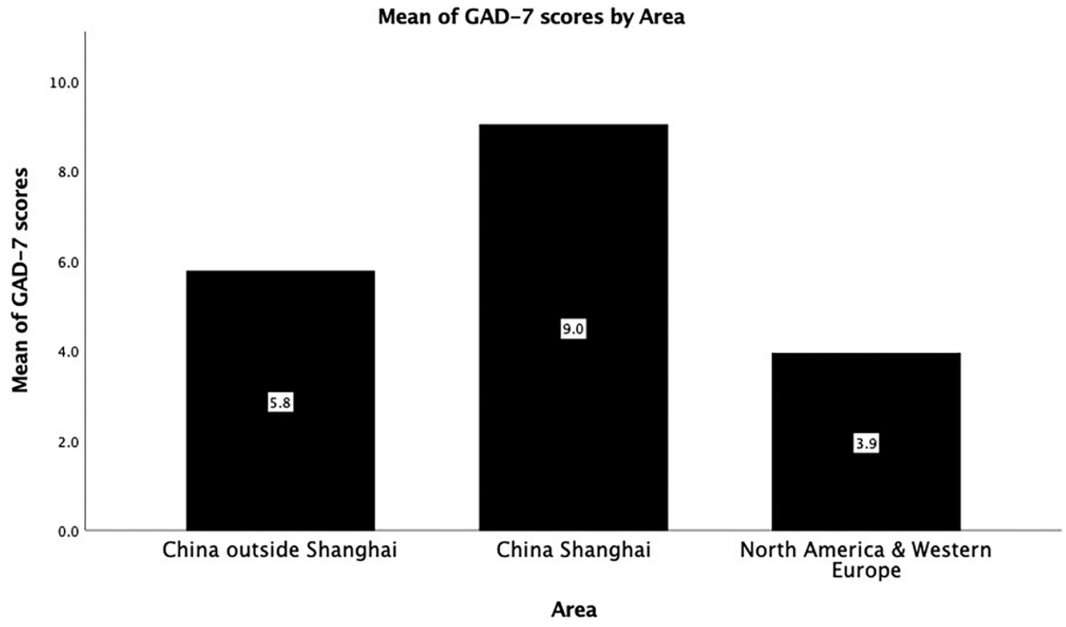

FIGURE 1
Mean of GAD-7 scores by area.

TABLE 3 Correlation between SATSO and GAD-7 scores among different areas.

Kendall's tau-b		SATSO in China (Shanghai) (n = 500)	SATSO in China outside Shanghai (n = 500)	SATSO in North America and Western Europe (n = 500)
GAD-7 scores	Correlation coefficient	0.44**	0.37**	−0.01
	Sig. (2-tailed)	0.00	0.00	0.70

N = 1,500. **Representing the correlation is significant at the 0.01 level ($p < 0.01$).
SATSO, Subjective attitude toward the sequelae of Omicron.

Admittedly, participants' mindsets toward the pandemic might differ due to different cultures (50). But in the context of the COVID-19 pandemic in today's advanced technological society, media outlets have been seen as useful means of spreading information about COVID-19 and measuring public attention toward COVID-19 in both China and the Western countries (37–39, 51, 52). Online COVID-19 infodemic (i.e., pandemic of misinformation), without prudent journalistic judgments of media content, could be easily and quickly disseminated and thus influence public opinions (39), therefore resulting in deadly consequences (51, 52). In addition, as we mentioned in the Introduction section, Chinese people's perceptions toward COVID-19 could largely rely on the propagation of information of COVID-19 through media outlets, in comparison with the residents in North America and Western Europe, where a virus co-existence policy with relatively few restrictions to the public resulted in a great number of people being affected with COVID-19; but meanwhile, these people were thus allowed to have an actual experience of how long-term COVID-19 impacts their body, rather than only acquiring relevant information *via* media reports. Hence, the propagation of information about COVID-19 should be concerned, especially for the Chinese public.

Over the course of the COVID-19 pandemic, researchers are still struggling with the after-effects of coronavirus as it continued to evolve. Nowadays, as the COVID-19 variants prior to Omicron have nearly fade away, investigating and discussing the potential sequelae of Omicron that is the most prevalent variant in the current pandemic situation is necessary (53). Nevertheless, due to the significant lag in the publication of studies relevant to COVID-19 sequelae, the findings of recently published articles may not be applied to the latest Omicron situation. For example, the study suggesting that COVID-19 could lead to greater reduction in brain gray matter thickness was conducted in 2021 when the participants involved in this study were infected with the earliest variant of COVID-19 rather than Omicron (54); meanwhile, these participants were unvaccinated and generally older. Therefore, it is difficult to match these sequelae with the current less threatening Omicron. But a very recently published article suggested that the

probability of Omicron causing long-term impacts to patients (4.5% of Omicron patients developed sequelae) was half that of Delta (10.8%) (55).

Some anecdotal findings reported by Chinese mass media indicated that most negative impacts of Omicron sequelae to human body were not reversible. However, that was not what previous studies actually found. For example, Zhao et al. suggested that mild Omicron sequelae such as slightly reduced attention and memory ability, which were even not perceived by participants themselves, were much improved over time (56). Similarly, another study followed the health status of patients with COVID-19 in Wuhan for 1 year after discharge from the hospital, and found that the after-effects of COVID-19 such as fatigue, sleeping disturbance and depression initially presented were improved greatly over time in these patients (57). Moreover, given that the study was conducted on the first batch of patients infected with COVID-19 in Wuhan, its findings were also not time-sensitive in the current context of Omicron.

Many anecdotal news online also stated that there was evidence that COVID-19 could induce male impotence. In fact, although a relevant study did suggest that COVID-19 may induce testicular damage, which could eventually result in decreased libido and fertility, the subjects involved in this study were animal rather than human patients; meanwhile, it was found that such negative impacts could be preventable by vaccination (58). However, when the findings of this study were reported by the mass media outlets, they overly exaggerated the impacts of COVID-19 by just saying "New study shows COVID-19 infection could cause testicular atrophy and reduced fertility in men." The lack of evidence for statements such as the effects of COVID-19 on fertility and intelligence is not only unfair and discriminatory to those infected with COVID-19, but also affects the psychological state of those who have never suffered COVID-19 infection and increases their anxiety level. Therefore, the mass media reports were misleading to the public, which should have been avoided as much as possible. Regarding the effectiveness of vaccination against long COVID-19, two studies by Ayoubkhani et al. demonstrated that people who completed two doses of vaccine were less likely to develop long-term sequelae after being infected with COVID-19 (59, 60).

Furthermore, it is also important to note that the COVID-19 sequelae are not necessarily related to the COVID-19 itself. More specifically, any influenza or infectious disease may also induce similar negative impacts as COVID-19. For instance, a cross-sectional study with a large French cohort suggested that the so-called sequelae of COVID-19 perceived by patients themselves may be more psychological or actually caused by other diseases than the laboratory-confirmed result of COVID-19 infection (61).

Another issue to note is that our study found around half of the Chinese participants (**Table 1**) having psychological fear toward friends infected with COVID-19, though no significant difference between such mindsets and their anxiety levels was found in terms of GAD-7 mean scores. Therefore, we should advocate avoiding whether implicitly or explicitly discriminating people infected with COVID-19 who have the potential to suffer from various degrees of psychological disorders due to surrounding pressures such as social rejection.

Overall, with the widespread vaccination around the world, threats of the COVID-19 pandemic have been weakened. As can be seen from the outbreak in Shanghai recently, a large number of asymptomatic patients, even confirmed cases, were mainly mild symptom patients. Given that the global pandemic has become the norm, a total zero-out policy is not desirable. What we should do is to face the COVID-19 bravely with a more open and inclusive mind. In the current article, it seems that the fear of Omicron after-effects is more frightening than the COVID-19 itself in Chinese population. Thus, policy makers should enhance the public's awareness of the latest change of pandemic situation, to eliminate unnecessary worries and reduce the psychological burden of Chinese people.

Limitation

The current study has several limitations. First, this study was a cross-sectional study that might restrict causal inference. Second, the sample size was not large enough, thereby limiting the generalizability of this study. Third, this study was based on self-reported responses of participants. Although the data derived from an online professional data collection platform, more study with more professional research methods in similar topics is needed to carry out in the future, when conditions are permitted. Finally, another limitation in this study is the fact that participants' media exposure was hard to track and measure, so a direct correlation between participants' perceptions toward COVID-19 or Omicron specifically resulted from exposure to media outlets and their anxiety levels could be biased and still needs more study to further demonstrate.

Conclusion

Currently, the global pandemic is subsiding as the novel coronavirus gradually evolves in a less harmful direction. However, due to the exaggeration about the long effects of Omicron by mass media outlets, which is currently the most prevalent variant of COVID-19, a variety of fears about Omicron long effects and a great deal of unpredictability about the future pandemic continue to plague people. In the current study we found that Chinese participants who were more worried about the after-effects of Omicron had higher levels of anxiety. Overall, although we still need to pay sufficient attention to COVID-19 and its long effects, we should take everything related to COVID-19 seriously based on the available scientific

evidence, and not easily believe exaggerated or even false reports in the mass media. Also, to eliminate unnecessary worries and reduce the psychological burden of Chinese people, policy makers should put sufficient efforts to enhance the public's awareness of the latest change of pandemic situation. In the future, more relevant studies are needed to reveal the long-term impacts of Omicron or subsequent variants of COVID-19.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval were not required for this study on human participants in accordance with the local legislation and institutional requirements. The participants were notified to provide their written informed consent online before participation in this study.

Author contributions

DS proposed the research idea, collected and analyzed the data from China, and wrote the initial manuscript. CL performed the literature search, provided the idea for the analysis, and collected the data from North America and Western Europe. SYL contributed to the substantial revisions of the manuscript in terms of reviewers' comments. YDZ checked the accuracy of the data analysis and was responsible for final proofreading and contributing to minor revisions of the latest manuscript. All authors have read and approved the final version of the manuscript and agreed with the order of the presentation of the authors.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Corrigendum: Increased anxiety from fear of Omicron in China as compared to North America and Western Europe: A cross-sectional Kendall's tau-b analysis using the generalized anxiety disorder 7-item questionnaire

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In the original article, there was a statistical error in the **Materials and Methods** section, page 4. The text read as "Eventually, a valid sample of 1,500 participants was analyzed collectively (892 females and 192 males; mean age = 26.74 years, SD = 3.81 years; age range: 18–34 years)." The statement has been corrected as follows:

"Eventually, a valid sample of 1,500 participants was analyzed collectively (688 females and 812 males; mean age = 26.74 years, SD = 3.81 years; age range: 18–34 years)."

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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Relationship between social support, anxiety, and depression among frontline healthcare workers in China during COVID-19 pandemic

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Background: Social support is an important factor affecting individual mental health. However, the relationship between social support and mental health in frontline healthcare workers (FHW) during the coronavirus disease 2019 (COVID-19) pandemic has garnered less attention. In this study, we aimed to investigate the level of social support and the prevalence of depression and anxiety in FHW during the COVID-19 pandemic and determine the factors affecting the relationship between social support, depression, and anxiety.

Methods: A cross-sectional study using an online survey was conducted to collect data from FHW between 15 February and 31 March 2020 in China. The data included demographic factors, Self-rated Depression Scale (SDS), Self-rated Anxiety Scale (SAS), and Social Support Rate Scale (SSRS). Spearman correlation test was performed to determine the correlation among SAS, SDS, and SSRS scores. Multiple linear regression analysis was performed to determine the relationship among demographic factors, social support, depression, and anxiety in FHW.

Results: Of all 201 participants, 44 (21.9%) had depressive symptoms and 32 (15.9%) had anxiety symptoms. The average total SSRS scores among FHW were lower than that of the norms of the Chinese general population (37.17 ± 7.54 versus 44.38 ± 8.38, $P < 0.001$). Marital status positively affected the SSRS score ($\beta = 7.395$, $P < 0.01$). Age over 40 years old negatively affected the SSRS score ($\beta = -5.349$, $P = 0.017$). The total SSRS score, subjective social support score, objective social support score, and support utilization score among FHW negatively correlated with the SAS score and SDS score ($P < 0.05$). A lower support utilization score was significantly associated with

high anxiety and depressive symptoms (β = −0.869, P = 0.024; β = −1.088, P = 0.035, respectively).

Conclusion: During the COVID-19 pandemic, FHW experienced depression, anxiety, and inadequate social support. The marital status and age had a major impact on social support. Social support was inversely associated with depression and anxiety. Improving the mental health of FHW by strengthening social support is crucial. Future studies are needed to investigate how to improve the level of social support and mental health condition of FHW facing public health emergencies in the future.

KEYWORDS

depression, anxiety, social support, COVID-19, frontline healthcare workers

Introduction

Since its outbreak in December 2019 in Wuhan, coronavirus disease 2019 (COVID-19) has posed a huge challenge to the healthcare system of China. On 29 January 2020, all 31 Chinese provinces declared public health emergencies and initiated lockdown policies in affected areas (1). As of 31 March 2020, 81,518 cases and 3,187 deaths were reported in China (2).

Amidst the development of the COVID-19 pandemic, frontline healthcare workers (FHW) globally were under tremendous pressure, and many suffered from psychological disorders (3), such as anxiety, depression, psychological stress response, and sleep disorders (4). When this online survey was conducted, the COVID-19 pandemic in China was still serious, with more than 2,400 confirmed cases and 139 deaths every day (5). FHW had to simultaneously prevent and treat the infection of COVID-19. The exhaustive work and risk of being infected by the virus caused a heavy psychological burden on FHW. Wearing protective equipment can relatively limit the communication of FHW. These factors can induce the presence of anxiety and depression among FHW during the COVID-19 pandemic. A cross-sectional study performed in the early stages of the COVID-19 outbreak reported that a significant proportion of FHW in China reported symptoms of depression (50.4%), anxiety (44.6%), insomnia (34.0%), and distress (71.5%) (6). Furthermore, anxiety symptoms can compromise work and frontline activities that can negatively affect private and social leisure activities (7). Previous studies focusing on the mental health reactions of healthcare workers during the acute phase of the COVID-19 pandemic reported that post-traumatic stress disorder, anxiety, and depression were associated with impairment in both work and social functioning (8, 9). FHWs are the direct providers of hospital services and are a key factor in controlling the pandemic (10). These psychological disorders affect the quality of life and health of FHW and also their professional performance, which greatly reduce their work efficiency and negatively affect the control of the COVID-19 pandemic.

Social support, which refers to the social connections, social integration, and major group relationships for individuals, is an important part of social psychology (11). Social support can enhance the protection of self-consciousness and effectively relieve the psychological disorders of individuals (12, 13). Lau proposed that social support is a crucial factor in alleviating stressful events and reducing their negative effects on the physical and mental health of individuals (14). Social support is associated with depression among health workers in developed countries (15, 16). Similarly, Chinese physicians had a higher prevalence of depressive symptoms and lower social support than the Chinese general population (17). A cross-sectional survey of Chinese doctors reported that social support is an important protective factor for the psychology of doctors. The more social support provided to doctors, the lower their depressive and anxiety symptoms (18). Another study also revealed that sufficient social support and training on positive coping skills can reduce anxiety in medical staff during the COVID-19 pandemic (19). Although these studies investigated the association between social support, depression, and anxiety among health workers, the relationship between social support and mental health among FHW during the COVID-19 pandemic was not investigated. The studies on psychological disorders of FHW in China mostly focused on epidemiological surveys (6, 20, 21). However, the relationship between social support and mental health among FHW during the COVID-19 pandemic has garnered less attention. The factors affecting the relationship between social support and mental health among FHW remains is yet to be investigated, which limits us from taking effective measures to help reduce psychological disorders, such as depression and anxiety, among FHW.

To bridge this gap, in this study, we aimed to investigate the level of social support and the prevalence of depression and anxiety among FHW during the COVID-19 pandemic and

determine the factors affecting the relationship between social support, depression, and anxiety. We hope that our research can help us better understand the psychological needs of FHW during the pandemic and provide a basis for government health departments to formulate effective psychological rehabilitation intervention policies.

Materials and methods

Ethical approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (No. ZE2020-036). This trial has been registered at the Chinese Clinical Trial Registry (No. ChiCTR2000029815). All participants provided their informed consent prior to their participation in the electronic questionnaire (with a "yes or no" question) to confirm their willingness to participate in this study. The data was stored on a cloud server accessible only to the main author.

Study design and participants

This cross-sectional study was conducted from 15 February to 31 March 2020 in China after the COVID-19 outbreak has been declared as a public health emergency of international concern. As the Chinese government advised the public to reduce their face-to-face interactions and tightened restrictions on the flow of people, potential participants were invited to complete an anonymous online questionnaire. The online questionnaire was developed using the SurveyStar[1] (Changsha Ranxing Information Technology Co., Ltd., Changsha, China). Next, we shared the questionnaire on the social media, including WeChat and Tencent QQ. The responses to the questionnaire were automatically collected into an EXCEL spreadsheet by the SurveyStar for further data analyses.

The inclusion criteria for the participants were as follows: (1) being a FHW; (2) age >18 years; (3) Chinese resident; (4) no history of mental illness; (5) submitted only one survey using the same IP address; and (6) volunteered to participate in this study. The exclusion criteria included the following: (1) working time on the frontline of COVID-19 prevention and control <1 week; (2) trainee, interns, external hired, or dispatched personnel; (3) refusal to participate in the survey; and (4) the time to complete the questionnaire being <5 min.

To determine the practicability of the online questionnaire, the constituent instruments were pilot-tested beforehand on a group of 20 FHW, and these individuals were excluded from the main study.

Survey development

Socio-demographic characteristics

Demographic and social data were self-reported by the participants, which included their age, gender, marital status (married or single), educational level (master's degree or above, bachelor's degree or lower), profession (doctor or nurse), seniority (primary, intermediate, or senior), and the number of days working at the frontline since COVID-19 outbreak (7–28, >28 days). The participants were asked whether they were currently working in one of the following three departments: fever clinics, isolation ward for suspected cases, and treatment ward for confirmed cases. The respondents who answered with a "yes" were defined as FHW and those who answered with a "no" were defined as second-line healthcare workers. The latter were excluded from this study.

Depressive symptoms

Depressive symptoms of FHW were assessed by the well-established Self-rated Depression Scale (SDS) (22). SDS is a widely recognized tool for evaluating depressive disorder (23). The score of each item was added and then multiplied by 1.25 as a total score ranged from 25 to 100, with a higher score indicating more depressive symptoms. The severity rating index for SDS were as follows: normal (25–52), mild (53–62), moderate (63–72), and severe (73–100). We categorized FHW with an SDS score ≥53 as having depressive symptoms. In this study, the Cronbach's alpha of SDS was 0.886.

Anxiety symptoms

Anxiety symptoms were assessed by using the Self-rated Anxiety Scale (SAS) (24, 25). An aggregate score of 20 items was multiplied by 1.25, with a higher score indicating more severe levels of anxiety. Anxiety score of <50 was considered normal, that of 50–60 was considered mild, that of 61–70 was considered moderate, and that >70 was considered severe. We set the cutoff point of SAS at 50 to suggest anxiety symptoms. In this survey, the Cronbach's alpha of SAS was 0.806.

Social support

Social support was assessed by using the Social Support Rate Scale (SSRS), which was designed to determine how

1 https://www.wjx.cn

much support respondents received from their family, friends, and social contexts (26, 27). SSRS consists of three subscales: subjective support (four items on the number of friends who offered assistance, relationship with neighbors, relationship with colleagues, and the level of support from family members), objective support (three items on the living conditions in the past year, problem-solving channels in emergency situations, and the sources of psychological comfort in the event of stress or resistance), and support utilization (three items on the way one expresses when in trouble, the way in which one seeks help when in trouble, and the willingness of participation in group activities). The total SSRS score is the sum of these three subscales scores, with a higher score indicating higher levels of social support (28). In this study, the Cronbach's alpha value of SSRS was 0.844.

Statistical analyses

The dataset was entered and analyzed using the statistical package for the social sciences (SPSS) version 25.0 (IBM Corp., Armonk, NY, United States). The following descriptive statistics were used, including frequencies (*n*), percentages (%), means, and standard deviations (SD).

Shapiro–Wilk test was performed to examine the normality. Reliability was assessed with Cronbach's alpha. One-sample mean test was performed to identify the difference in the SSRS score between FHW and the norms of Chinese general population. One-way analysis of variance was conducted to identify the difference in the SDS, SAS, and SSRS of the FHW based on the demographic factors. Spearman correlation analyses were performed to examine the relationship among the scores of SAS, SDS, and SSRS.

Multiple linear regression analysis was performed to examine the association between social support and demographic factors. The dependent variable was the total SSRS score, and the independent variables included age, marital status, and seniority. We also conducted multiple linear regression analysis to identify the relation among social support and the SDS and SAS scores. The dependent variable was the SDS and SAS scores. The independent variables included subjective social support score, objective social support score, support utilization score, and the total SSRS score. The regression model was statistically significant ($P < 0.05$), indicating a linear correlation between the dependent and independent variables. All tolerance values were >0.1, and the VIF value was <10, which indicated that no data had multicollinearity (29). Regression coefficient estimates (β), standard error (SE) of β, 95% confidence intervals (CIs) of β, and *P*-values were also analyzed. $P < 0.05$ was considered to indicate statistical significance.

Results

Sample characteristics

A total of 211 participants answered questionnaires in the survey, of which 201 fulfilled the study inclusion criteria, giving an effective response rate of 95.3%. Of the 201 participants (mean age = 33.31 years, SD = 7.12 years), 100% worked on the frontline during the COVID-19 pandemic, 43.3% were between the ages of 30 and 39, 74.6% were women, 58.2% were married, and 82.1% had a bachelor's degree or lower. In terms of professionally, 63.2% were registered nurses, 55.2% held a primary professional title, 47.8% of healthcare workers were affiliated with the suspected case isolation ward unit, and 73.6% worked on the frontline for 7–28 days. The socio-demographic and clinical characteristics of the participants are presented in **Table 1**.

Assessment of depression and anxiety

Among 201 FHW, the mean scores of SAS and SDS were 40.98 (SD = 8.20) and 43.30 (SD = 11.38), respectively. A total of 44 (21.9%) participants self-reported depressive symptoms, and 32 (15.9%) participants self-reported anxiety symptoms (**Table 1**).

In terms of depression and anxiety, the participants were distributed across the three levels of severity. Based on the data of this survey, 44 participants reported depressive symptoms, 32 (72.7%) reported mild depression, 9 (20.5%) reported moderate depression, and 3 (6.8%) reported severe depression. Of 32 participants with anxiety symptoms, 29 (90.6%) reported mild anxiety, 2 (6.3%) reported moderate anxiety, and 1 (3.1%) reported severe anxiety (**Figure 1**).

Assessment of social support

The average scores of SSRS, subjective support, objective support, and support utilization were 37.17 (SD = 7.54), 20.20 (SD = 3.97), 9.41 (SD = 3.47), and 7.56 (SD = 2.02), respectively. Shapiro–Wilk test showed that the total SSRS score and three subscales scores of the SSRS were normally distributed ($P > 0.05$). The one-sample mean test showed that the total SSRS score and three subscales scores of the SSRS among FHW were lower than that of the norms of the Chinese general population (30), respectively ($P < 0.01$) (**Table 2**).

TABLE 1 The socio-demographic and clinical characteristics of the participants.

Characteristic	Total sample	Depressive symptoms	Anxiety symptoms
Participants	201 (100%)	44 (21.9%)	32 (15.9%)
Age, *n* (%)			
20–29	74 (36.8%)	13 (29.55%)	10 (31.25%)
30–39	87 (43.3%)	21 (47.73%)	12 (37.50%)
>40	40 (19.9%)	10 (22.72%)	10 (31.25%)
Gender, *n* (%)			
Male	51 (25.4%)	11 (25.00%)	10 (31.25%)
Female	150 (74.6%)	33 (75.00%)	22 (68.75%)
Marital status, *n* (%)			
Single	84 (41.8%)	16 (36.36%)	12 (37.50%)
Married	117 (58.2%)	28 (63.64%)	20 (62.50%)
Education, *n* (%)			
Bachelor's degree or lower	165 (82.1%)	39 (88.64%)	27 (84.38%)
Master's degree or above	36 (17.9%)	5 (11.36%)	5 (15.62%)
Profession, *n* (%)			
Doctor	74 (36.8%)	12 (27.27%)	11(34.37%)
Nurse	127 (63.2%)	32 (72.73%)	21(65.63%)
Seniority, *n* (%)			
Primary	111 (55.2%)	25 (56.82%)	14 (43.75%)
Intermediate	58 (28.9%)	13 (29.55%)	13 (40.63%)
Senior	32 (15.9%)	6 (13.63%)	5 (15.62%)
Department, *n* (%)			
Fever clinics	83 (41.2%)	21 (47.73%)	14 (43.75%)
Isolation ward for suspected cases	96 (47.8%)	18 (40.91%)	15 (46.87%)
Treatment ward for confirmed cases	22 (11.0%)	5 (11.36%)	3 (9.38%)
Number of days on the frontline since the COVID-19 outbreak, *n* (%)			
7–28 days	148 (73.6%)	27 (61.36%)	24 (75.00%)
>28 days	53 (26.4%)	17 (38.64%)	8 (25.00%)
SDS score, mean ± SD	43.30 ± 11.38	60.02 ± 6.19	
SAS score, mean ± SD	40.98 ± 8.20		54.47 ± 5.79

SAS, Self-rated Anxiety Scale; SDS, Self-rated Depression Scale; SD, standard deviation.

The association between demographic factors and social support, depression, and anxiety

One-way analysis of variance showed no significant difference in the effect of demographic factors on depressive and anxiety symptoms (Table 3). However, a one-way analysis of variance showed that FHW within the age of 30–39 years old had a higher SSRS score compared with the younger FHW (39.22 ± 7.45 versus 34.62 ± 6.93, $P < 0.01$). Moreover, the total SSRS score of married FHW was higher than that of unmarried FHW (39.92 ± 6.73 versus 33.33 ± 6.93, $P < 0.01$). Compared with FHW with primary titles, FHW with senior titles had a lower total SSRS score (39.34 ± 7.34 versus 35.64 ± 7.72, $P = 0.013$), whereas FHW with intermediate titles had a higher total SSRS score than those with senior titles (38.90 ± 6.70 versus 35.64 ± 7.72, $P = 0.007$) (Table 3).

Multiple linear regression analysis was performed to investigate the association between social support and demographic factors. The regression model was statistically significant [$F(5,195) = 11.216$, $P < 0.001$], which suggested that a linear correlation existed between the dependent and independent variables. In this study, all tolerance values were greater than 0.1 (minimum 0.3) and the VIF was less than 10 (maximum 3.5), which indicated that all data had no multicollinearity. Multiple linear regression analysis showed that being married positively affected the SSRS score ($\beta = 7.395$, $P < 0.01$), and age over 40 years old negatively affected the SSRS score ($\beta = -5.349$, $P = 0.017$). Multiple linear regression analysis also showed that age, marital status, and seniority were

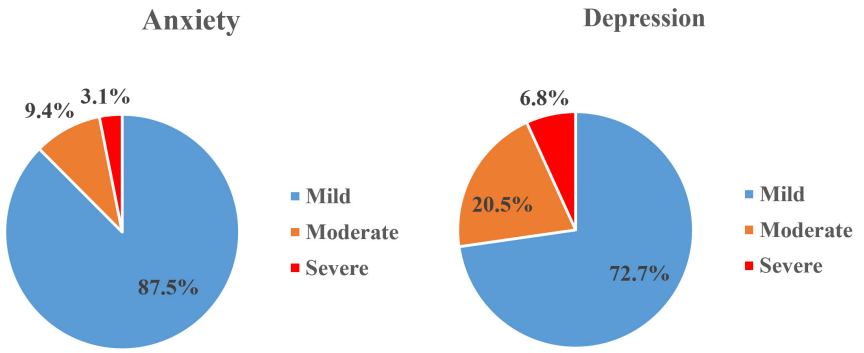

FIGURE 1
The distribution of levels of severity on depression and anxiety (prevalence of depressive and anxiety symptoms based on a cutoff score of 53 on SDS and 50 on SAS, respectively. Of 201 participants, 44 participants self-reported with mild-severe depressive symptoms and 32 participants self-reported with mild-severe anxiety symptoms).

TABLE 2 The difference of social support scores among frontline healthcare workers and the norms of Chinese general population.

Variable	Total sample (n = 201)	Norms of general population	t	P-value
Total SSRS score, mean ± SD	37.17 ± 7.54	44.38 ± 8.38	−13.560	<0.001
Subjective social support score, mean ± SD	20.20 ± 3.97	23.81 ± 4.75	−12.896	<0.001
Objective social support score, mean ± SD	9.41 ± 3.47	12.68 ± 3.47	−13.341	<0.001
Support utilization score, mean ± SD	7.56 ± 2.02	9.38 ± 3.40	−12.781	<0.001

SD, standard deviation; SSRS, Social Support Rate Scale.

associated with social support, which explained 20.3% of all variance (Table 4).

The association between social support and depression and anxiety

Spearman correlation test showed that the total SSRS score, subjective social support score, objective social support score, and support utilization score among FHW were all negatively correlated with the SAS score and SDS score ($P < 0.05$) (Table 5). Multiple linear regression analysis suggested that a lower support utilization score was respectively significantly associated with high anxiety and depressive symptoms ($\beta = -0.869$, $P = 0.024$; $\beta = -1.088$, $P = 0.035$, respectively). Multiple linear regression analysis also showed that the total SSRS score, objective social support score, and support utilization score were associated with anxiety and depressive symptoms, which explained 8.9 and 14.9% of all variance, respectively (Tables 6, 7).

Discussion

To the best of our knowledge, this is the first study to investigate the relationship between the levels of social support and the prevalence of depression and anxiety among FHW during the COVID-19 pandemic in China. FHW are the direct providers of hospital services and the main force in controlling COVID-19. Understanding their level of social support and the relationship between psychological impact and social support can help Chinese hospital management and health policymakers take effective measures to further improve the mental health well-being of FHW, thus improving their professional performance and work efficiency.

Prevalence of depression and anxiety

This study showed that during the COVID-19 pandemic, the prevalence of depressive and anxiety symptoms among FHW was 21.9 and 15.9%, respectively. However, using the same measurement as in our study, the prevalence of depressive and anxiety symptoms among FHW in the early stages of the COVID-19 pandemic was 35.8 and 22.4% (31), respectively, which was significantly higher than the population surveyed in our study. This is most likely associated with the deployment of psychological assistance services by the Chinese government. On 26 January 2020, the Ministry of Health of the Chinese Government issued a guideline for emergency psychological crisis intervention and counseling (32). On 2 February 2020, the state council of China set up

TABLE 3 Difference in total SSRS, SDS, and SAS based on demographic characteristics.

Variable	Total SSRS score (mean ± SD)	*F*	*P*-value	SAS score (mean ± SD)	*F*	*P*-value	SDS score (mean ± SD)	*F*	*P*-value
Total sample (*n* = 201)	37.17 ± 7.54			40.98 ± 8.20			43.30 ± 11.38		
Age									
20–29 (*n* = 74)	34.62 ± 6.93	7.982	<0.001	40.70 ± 7.45	0.780	0.460	42.62 ± 10.49	0.651	0.523
30–39 (*n* = 87)	39.22 ± 7.45[a]			40.55 ± 8.52			43.05 ± 11.76		
>40 (*n* = 40)	37.43 ± 7.59			42.43 ± 8.87			45.10 ± 12.22		
Gender									
Male (*n* = 51)	38.75 ± 7.52	3.016	0.084	41.92 ± 9.56	0.899	0.344	43.67 ± 11.25	0.071	0.790
Female (*n* = 150)	36.63 ± 7.50			40.66 ± 7.70			43.17 ± 11.46		
Marital status									
Single (*n* = 84)	33.33 ± 6.93	45.704	<0.001	40.68 ± 8.70	0.194	0.660	43.11 ± 10.90	0.041	0.841
Married (*n* = 117)	39.92 ± 6.73			41.20 ± 7.86			43.44 ± 11.76		
Education									
Bachelor's degree or lower (*n* = 36)	37.14 ± 7.51	0.001	0.979	39.11 ± 10.33	2.291	0.132	41.72 ± 11.30	0.840	0.360
Master's degree or above (*n* = 165)	37.18 ± 7.57			41.39 ± 7.64			43.64 ± 11.40		
Profession									
Doctor (*n* = 74)	38.03 ± 7.24	1.520	0.219	39.82 ± 9.04	2.340	0.128	41.72 ± 10.80	2.278	0.133
Nurse (*n* = 127)	36.67 ± 7.70			41.65 ± 7.63			44.22 ± 11.65		
Seniority									
Primary (*n* = 32)	39.34 ± 7.34[b]	5.362	0.005	39.72 ± 8.38	0.448	0.639	42.09 ± 12.23	0.470	0.626
Intermediate (*n* = 58)	38.90 ± 6.70[b]			41.26 ± 8.66			42.66 ± 10.80		
Senior (*n* = 111)	35.64 ± 7.72			41.20 ± 7.95			43.98 ± 11.48		
Department									
Fever clinics (*n* = 83)	37.67 ± 8.34	1.277	0.281	41.07 ± 8.33	1.053	0.351	43.66 ± 12.00	0.194	0.824
Isolation ward for suspected cases (*n* = 96)	36.35 ± 7.13			41.44 ± 8.33			43.29 ± 11.40		
Treatment ward for confirmed cases (*n* = 22)	38.82 ± 5.75			38.64 ± 7.04			41.95 ± 9.03		
Number of days on the frontline since the COVID-19 outbreak									
7–28 days (*n* = 148)	37.20 ± 7.47	0.011	0.916	40.90 ± 8.70	0.055	0.815	42.89 ± 11.33	0.739	0.391
>28 days (*n* = 53)	37.08 ± 7.80			41.21 ± 6.69			44.45 ± 11.56		

One-way analysis of variance showed age, marital status, seniority had an effect on total SSRS score. SAS, Self-rated Anxiety Scale; SDS, Self-rated Depression Scale; SD, standard deviation; SSRS, Social Support Rate Scale. [a]Compared with participants with 20–29 years old, $P < 0.01$. [b]Compared with participants with senior title, $P < 0.05$.

TABLE 4 Regression analysis of the effects of demographic factors on social support.

Variable	Unstandardized coefficients		Standardized coefficients	*t*	*P*-value	95% confidence interval for β	
	β	SE				Lower bound	Upper bound
Constant	34.129	1.670		20.432	<0.001	30.834	37.423
Age (ref. 20–29)							
30–39	−0.370	1.466	−0.024	−0.252	0.801	−3.262	2.522
>40	−5.349	2.224	−0.284	−2.405	0.017	−9.735	−0.963
Marital status (ref. single)							
Married	7.395	1.325	0.485	5.581	<0.001	4.782	10.008
Seniority (ref. intermediate)							
Senior	2.236	1.788	0.109	1.250	0.213	−1.29	5.761
Primary	−0.716	1.441	−0.047	−0.497	0.620	−3.559	2.127
R^2	0.223						
Adjusted R^2	0.203						

TABLE 5 Correlations between social support, anxiety, and depression.

Variables	SDS		SAS	
	r	*P*-value	*r*	*P*-value
Total SSRS score	−0.345	<0.001	−0.222	0.002
Subjective social support score	−0.260	<0.001	−0.156	0.027
Objective social support score	−0.257	<0.001	−0.176	0.013
Support utilization score	−0.335	<0.001	−0.268	<0.001

SAS, Self-rated Anxiety Scale; SDS, Self-rated Depression Scale; SSRS, Social Support Rate Scale.

TABLE 6 Regression analysis of the effects of social support on depression.

Variables	β (SE)	95% CI	*P*-value	Adjusted R^2
Objective social support score	−0.066 (0.396)	−0.848, 0.715	0.867	0.149
Support utilization score	−1.088 (0.513)	−2.099, −0.076	0.035	
Total SSRS score	−0.353 (0.222)	−0.789, 0.084	0.113	

β, the coefficients; CI, confidence interval; SE, standard error; SSRS, Social Support Rate Scale.

TABLE 7 Regression analysis of the effects of social support on anxiety.

Variables	β (SE)	95% CI	*P*-value	Adjusted R^2
Objective social support score	−0.039 (0.296)	−0.622, 0.544	0.896	0.089
Support utilization score	−0.869 (0.382)	−1.624, −0.115	0.024	
Total SSRS score	−0.136 (0.165)	−0.462, 0.190	0.412	

β, the coefficients; CI, confidence interval; SE, standard error; SSRS, Social Support Rate Scale.

a nationwide psychological assistance hotline to help people suffering from psychological disorders due to the epidemic (33). These programs are not only for patients with COVID-19 and the general public but also for all healthcare workers. Participants in this study received psychological assistance services before submitting questionnaires, which can reduce the prevalence of depression and anxiety.

Factors affecting the level of depression and anxiety

Our findings showed that no significant difference was found in the effect of demographic factors (such as age, gender, seniority, and education level) on depression and anxiety symptoms. The main reasons can be related to the small sample size of this study and the relatively low proportion of FHW with depression and anxiety. Many FHW experiencing symptoms of anxiety and depression had mild degrees of depression and anxiety in our study. Among all the participants, only 12 (27.3%) had moderate and severe depression, and 3 (9.4%) had moderate and severe anxiety. A previous study reported that the anxiety levels in health workers did not vary significantly with age, education, and marital status (34). However, a recent meta-analysis revealed the prevalence of anxiety and depression was higher among females and nursing staff than among males and doctors during the COVID-19 pandemic (3). Nurses, FHW, female, young, and intermediate seniority were associated with a severe degree of depression and anxiety (6, 35). Furthermore, a significant causal relationship was found between depression and age and working on the frontline (36). Another study reported that working in an isolation ward or fever clinic was an independent risk factor for depression and anxiety among frontline pediatric nurses, whereas age and education level did not have any significant effect on depression and anxiety (37). The effect of demographic factors on depression and anxiety is controversial and more rigorously designed studies are required to further clarify this issue.

Level of social support

Our study revealed that the total SSRS score of FHW was significantly lower than that of the general population. The three dimensions of social support (namely subjective social support, objective social support, and support utilization) of FHW were all significantly lower than the Chinese general population. In SSRS, subjective social support refers to the support received from family, friends, and colleagues. During the COVID-19 pandemic, the government-imposed quarantine policies and increased workloads limited the time that FHW could spend with family members and friends. Objective support refers to any type of visible or actual social support, especially economic assistance, received from any source, including the government,

non-governmental organizations, religious groups, and local communities (38). The low social status of healthcare workers in China can limit their access to objective social support beyond family members (39). The lockdown policies imposed by the government can also limit their participation in community activities, which made it difficult for them to obtain community help. Support utilization refers to the degree of willingness to seek social support. Fear of stigma can make FHW reluctant to seek outside support (40). Moreover, excessive workloads and minimal vacations can also lead to extreme fatigue for FHW, which can limit their willingness to join in social interactions during breaks (41).

Correlation between social support and depression and anxiety

We also found a negative correlation between the levels of social support and the severity of depressive and anxiety symptoms. The participants in our study who reported higher levels of social support were less likely to have symptoms of depression and anxiety, which indicated that social support is an important protective factor for the mental health of FHW. This was consistent with the results from previous studies (42, 43).

Subjective social support reflects the personal experience and feelings of social support (44). People with higher subjective social support score indicates that they receive adequate support, understanding, and respect from their family, friends, and colleagues. High subjective social support can help individuals to reduce loneliness and build a positive self-image, self-efficacy, and self-esteem, thus bringing more understanding, respect, courage, and professional achievements to themselves (45), which has a positive effect on reducing depression and anxiety of FHW.

Objective social support emphasizes the existence of visible social support (46). Those who scored higher on objective social support indicated that they received more visible help and support from the government, local communities, and non-governmental organizations. It also means they have extensive social networks. A high level of objective social support helps individuals to reduce the stress in work and life, and maintain good mental health, which can decrease the depressive and anxiety symptoms in FHW. Moreover, a wide social network can decrease the perceived threat of stressful events among FHW and reduce the physical reactions induced by stress, which also has a positive effect on reducing anxiety and depressive symptoms (47).

High social support utilization indicates a greater willingness to seek social support. This usually manifests as an emotional outpouring to family or friends or seeking help by participating in activities organized by the local community or religious groups. In our study, the higher the social support utilization of FHW, the less likely they were to have symptoms of depression and anxiety. This is consistent with the finding that a better connection with others can mitigate the harmful effects of stressful life events (48).

Factors affecting the level of social support

In the present study, the level of social support for FHW positively correlated with age. One possible reason could be that healthcare workers over 30 years are more likely to have experienced severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS) outbreaks; therefore, they have more experience in seeking social support in the COVID-19 pandemic (49). Moreover, being older also means they have a wider social network and more access to social support than younger people (less than 30 years old). Individuals who had more social support generally had better mental health than those who had less (50).

Our findings also showed that being single was associated with a low level of social support among FHW. One possible reason is that married healthcare workers have higher quality and wider social networks than single healthcare workers because they can receive additional social support from their spouse and spouse's family (51). These results are consistent with the study by Jaffar Abbas to some extent (52).

Interestingly, despite previous research showing differences in social support between male and female healthcare workers (17), our study showed that gender does not affect the level of social support. This can be because both male and female healthcare workers have longer working hours during the COVID-19 pandemic. Therefore, they did not have sufficient time to participate in family and social activities to seek social support (53). This may also explain why no difference was found in the social support between nurses and doctors in this study.

The results of this study showed that the department where FHW work and how long they worked on the frontline did not affect their social support because FHW feel so exhausted during the COVID-19 pandemic that they were reluctant to seek social support through social and family activities (54).

Previous studies have reported that healthcare workers with high education levels and seniority will receive more social support from patients and the social environment because of their high professional level and rich experience (55). However, the result of the present study showed that education level and seniority do not affect the social support of FHW. Further study is required to explain this phenomenon.

Policy implications

Based on our findings, during COVID-19 pandemic, policy makers should: (1) reduce the working hours and workload of

FHW and give them more time to participate in social and family activities; (2) pay more attention to the mental health of unmarried and young FHW and extend more help to alleviate the symptoms of depression and anxiety.

Limitations

This study has several limitations. First, this study used self-report measures, hence there was a risk of information bias. Second, our study was a cross-sectional study that limited our ability to make statements on causality. In the absence of further follow-up studies, caution should be exercised regarding causality. Third, the income level and religious belief of FHW were not considered in this study, which has a certain relationship with social support. Further prospective and longitudinal studies with a large sample size are needed to assess the impact of social support levels on the mental health in the context of COVID-19 pandemic.

Conclusion

In this study, we showed that 21.9 and 15.9% of FHW had depressive and anxiety symptoms, respectively. There was lower social support among FHW in comparison to the Chinese general population during the COVID-19 pandemic. The marital status and age had a major effect on social support. Social support was inversely associated with depression and anxiety. These findings signify that social support plays an important role in mental health, and health policymakers should pay more attention to the psychological status of FHW. Efforts should also be made to address their low level of social support, to reduce adverse psychological outcomes among FHW. More studies are required to determine how to improve the level of social support and mental health condition of FHW facing public health emergencies in the future.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (No. ZE2020-036). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

JZ and LL designed the study. JZ, LZ, and HC were responsible for the development and distribution of questionnaire. XY and XW were responsible for data auditing and data cleaning. JZ, CC, and LL analyzed and interpreted the data. CC and JZ revised the manuscript on the basis of comments from other authors. All authors have read and approved the final manuscript.

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Conflict of interest

The authors declare that this study received support from Changsha Ranxing Information Technology Co., Ltd. The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article, or the decision to submit it for publication.

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Dynamic changes in mental health status related to the COVID-19 pandemic among health care workers and inpatients in China

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Background: Exposure to coronavirus disease 2019 (COVID-19) can cause severe mental health problems, the dynamics of which remain unclear. This study evaluated the mental status of frontline health care workers (FHWs) and suspected infected patients (SIPs) during different periods of the COVID-19 outbreak.

Materials and methods: Demographic and psychological data were collected through a cross-sectional survey of 409 participants in a hospital from 20 January to 7 August 2020. COVID-19 outbreaks were divided into three periods owing to the time, place, and scale, including the national outbreak period (a nationwide pandemic period from 20 January to 8 April 2020), sporadic period (a stable period from 9 April to 10 June), and local epidemic period (a local pandemic in Beijing from 11 June to 7 August 2020). Acute psychological disorders (APDs), including symptoms of anxiety and depression, were assessed using the Zung Self-Rating Anxiety/Depression Scale (SAS/SDS).

Results: A total of 206 FHWs and 203 SIPs completed the electronic questionnaire. Overall, the prevalence rates of anxiety and depression among SIPs were 3.9 and 19.4%, respectively, while significantly higher prevalence rates (17.7 and 25.1%) were found among FHWs, P-value < 0.05. Psychological status among SIPs did not differ significantly across the three periods. The FHWs were more vulnerable, as their SAS and SDS scores and almost all the dimension scores were significantly higher during the local epidemic period than during the national outbreak and sporadic periods (all P-values < 0.001). The prevalence of anxiety (34.41%) and depression (41.94%) was significantly higher during the local epidemic period ($P < 0.001$). Logistic and linear mixed models showed that age, sex, and doctor-patient ratio especially, independently influenced most dimension scores of SAS and SDS among FHWs ($P < 0.05$).

Conclusion: Compared to the COVID-19 epidemic at the national level, the local epidemic had a greater influence on FHWs' mental health. More attention should be given to the workload of FHWs.

KEYWORDS

COVID-19, anxiety, depression, healthcare workers, mental health

Introduction

Coronavirus disease 2019 (COVID-19) currently represents an unprecedented threat to human health worldwide (1, 2). The first cases of this novel coronavirus (3, 4) were reported in Wuhan, the capital city of Hubei Province, China, in December 2019. Subsequently, the virus was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organization. The disease has a very strong infectious ability, such that it rapidly spread within a few months and finally became a worldwide health threat. The World Health Organization announced that as of 30 March 2021, 126,372,442 cases had been diagnosed, and 2,769,696 persons had died from COVID-19 due to the high mortality rate and lack of effective treatment (5). The primary routes of transmission include short-distance person-to-person contact, respiratory droplets, and aerosols. The pandemic has relentlessly affected normal social order, caused social panic, and seriously influenced public mental health (6), especially for those frequently exposed to high-risk environments.

Frontline health care workers (FHWs) are the most important force in preventing the spread of COVID-19 and protecting public health (7). However, due to factors such as direct exposure to infectious individuals, a shortage of protective equipment, prolonged separation from family and friends, and even stigmatization (8), FHWs often experience acute psychological disorders (APDs), such as anxiety and depression (9–11). As early as May 2020, the International Council of Nurses reported that more than 90,000 medical workers had been infected with COVID-19. This figure is likely to be conservative because countries were busy combatting the pandemic. Studies (12, 13) have shown that during the outbreak of SARS and Middle East respiratory syndrome (MERS), many frontline staff were infected in their workplaces, which often provoked their loss of emotional control and finally the emergence of APDs.

Abbreviations: APDs, acute psychological disorders; COVID-19, coronavirus disease 2019; FHWs, frontline health care workers; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome; SAS, the Zung Self-Rating Anxiety Scale; SDS, the Zung Self-Rating Depression Scale; SIPs, suspected infected patients.

The effective control of the COVID-19 outbreak in Wuhan was followed by a short period of tranquility. However, the calm soon ended in June 2020 with a local outbreak in the Xinfadi Agricultural Wholesale Market in Fengtai District, Beijing. At this time, increasing numbers of medical staff devoted themselves to handling the drastically increasing number of suspected infected patients (SIPs). The state of the spread of COVID-19 worldwide is not positive. Such a serious situation requires not only effective treatment programs but also more medical staff on the frontlines to combat the pandemic. Although doctor-patient mental health is a concern among scholars, the periods covered in most studies are relatively short (3, 14). Therefore, this study investigated the dynamic changes in APDs caused by the COVID-19 pandemic among health care workers and inpatients over a relatively long period, with the main purpose of providing important evidence for psychological interventions.

Materials and methods

Study design, participants, and data collection

This study was a cross-sectional survey conducted from 20 January to 7 August 2020, to observe the different psychosocial status of FHWs and SIPs during outbreaks of COVID-19 (**Figure 1**). During this time, a total of 503 FHWs were sent to isolation wards to combat the COVID-19 epidemic, each of whom worked in a totally closed environment for 3 weeks. According to the COVID-19 prevention policy, 914 consecutive SIPs were hospitalized in the isolation ward for a definitive diagnosis. A total of 41% of FHWs and 29% of SIPs in our hospital during this period were sampled for the psychological health status survey. All the data were collected by questionnaire on a professional online assessment platform.[1] Participants completed anonymous self-evaluation forms in the Mini Program provided by WeChat APP linked to the survey website using their own cell phones with each patient submitting questionnaire only once. The exclusion criteria included old age

1 www.wjx.cn

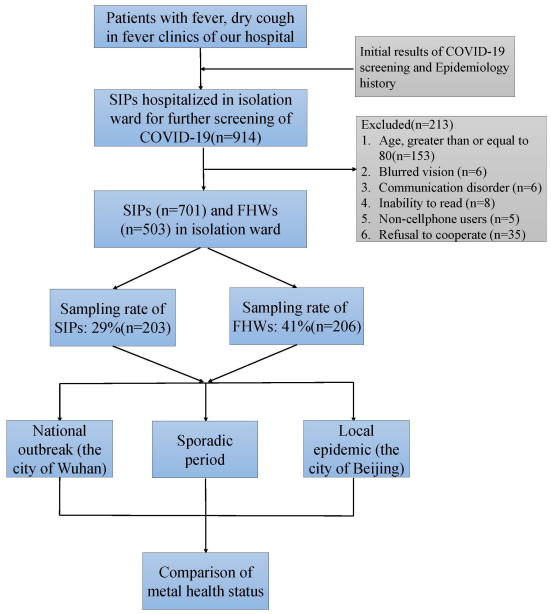

FIGURE 1
Consolidated Standards of Reporting Trials (CONSORT) diagram of the study. *COVID-19*, coronavirus disease 2019; *FHWs*, frontline health care workers; *SIPs*, suspected infected patients.

(80 years or above), blurred vision, communication disorders, illiteracy, non-use of cell phones, or refusal to cooperate. All participants were enrolled from isolation wards in Beijing Friendship Hospital, which is a third-level grade A general hospital in Beijing affiliated with Capital Medical University. During the COVID-19 outbreak period, the isolation wards mainly received patients with suspected infection from fever clinics. SIPs were screened by throat swab nucleic acid tests at least twice with an interval of 24 h. The results were reviewed by the team of chief examiners. If COVID-19 infection was confirmed, the infected patients were transferred to a designated hospital for further treatment. The other patients were released from the isolation wards. All the enrolled participants signed informed consent forms, and the study was approved by the Ethics Committee of Beijing Friendship Hospital (2020-P2-161-01).

The demographic characteristics included age, sex, area of residence (Fengtai District or other districts), education status (high school or below, bachelor's degree, master's degree, and doctoral degree), marital status (single, married, and divorced), and number of children in the participant's family (no children, one or more children). Participants were classified into three groups according to the enrolment date: national outbreak period, sporadic period and local epidemic period (**Figure 2**). The COVID-19 outbreak in Wuhan lasted from 20 January to 8 April 2020, and the number of local infected cases in Beijing increased during this period, which was defined as the national outbreak period. From 9 April to 10 June 2020, the epidemic in Wuhan was effectively controlled, and the number of local confirmed cases in Beijing remained stable, without a remarkable increase. This period was defined as the sporadic period. From 11 June to 7 August 2020, a new COVID-19 outbreak occurred in the Xinfadi Agricultural Wholesale Market in Fengtai District, Beijing, and the number of cases increased rapidly. This period was called the local epidemic period.

Assessment criteria

The symptoms of anxiety and depression were assessed with the Zung Self-Rating Anxiety/Depression Scale (SAS/SDS) (15, 16). These scales have been widely applied in clinical practice and scientific research, showing good reliability and convincing results in the Chinese population (17–19). The SAS and the SDS both include 20 items, with each item scored on a scale from 1 to 4, indicating none or a little of the time, some of the time, a good part of the time, and most or all of the time. The participants responded according to their psychological and physical symptoms within the past week. According to convention in China, the threshold score of anxiety on the self-reported scale is 50. Scores in the range of 50–59 indicate slight anxiety, scores from 60 to 69 indicate moderate anxiety, and scores above 70 indicate severe anxiety. For depression, the cut-off score is 53, with scores in the range of 53–62 implying slight depression, scores ranging from 63 to 72 indicating moderate depression, and scores above 73 indicating severe depression.

Physical symptoms of anxiety and depression can manifest in multiple systems, such as the cardiovascular, digestive, respiratory, skeletal and muscle, urinary, and reproductive systems. The related physical complaints are often composed of factors in several dimensions. The SAS/SDS includes only the abovementioned physical symptoms. Therefore, the SAS/SDS is an appropriate instrument for dimensional analysis and theoretically supports the detection of the cause of mental disease.

A four-factor structure of the SAS/SDS (20, 21), which is generally stable and significantly correlated with relevant variables, was adopted in this study. The SAS contained four factors: anxiety and panic (items 1, 2, 3, 4, 18), somatic control (items 5, 9, 13, 17, 19), vestibular sensations (items 6, 10, 11, 12, 14), and gastrointestinal/muscular sensations (items 7, 8, 15, 16, 20). The SDS also consisted of four dimensions: core depression (items 1, 3, 6, 14, 17, 18, 19, 20), cognitive depression (items 10, 11, 12, 16), anxiety (items 4, 13, 15), and somatic control (items 5, 7, 9). Items 2 and 8 were not included.

Statistical analysis

The independent continuous variables, including age, SAS score, SDS score and dimension score, were described as means

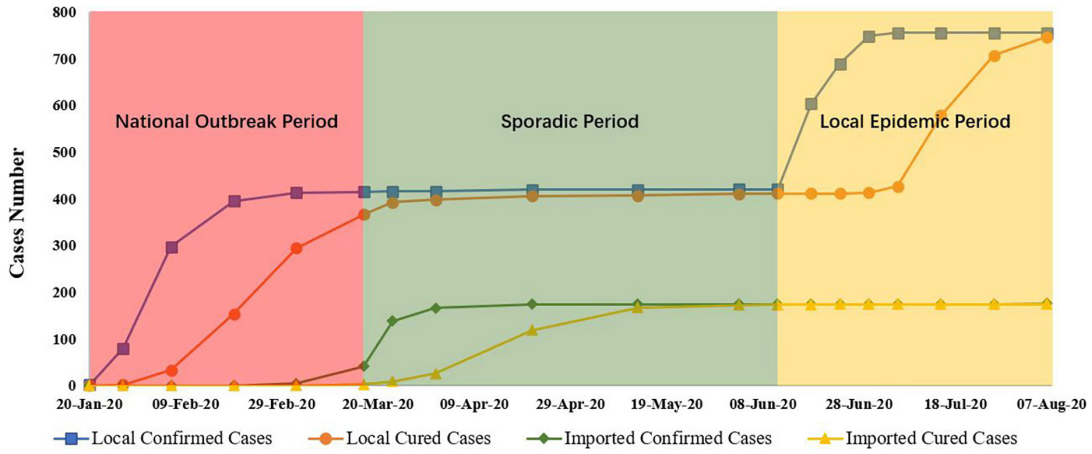

FIGURE 2
COVID-19 cases during the national outbreak, sporadic, and local epidemic periods in Beijing. Data were obtained from the Beijing Municipal Health Commission (available at http://wjw.beijing.gov.cn/). *COVID-19*, coronavirus disease 2019.

with standard deviations (SDs) and analyzed by ANOVA tests among the three-period groups. Categorical variables, including sex, area of residence, education status, marital status, and the number of children, were described as frequencies (%) and analyzed by the chi-square test or Fisher's exact test. Bonferroni-adjusted tests were used for multiple comparisons. Univariate and stepwise multivariate logistic regression models were used to calculate the factors influencing anxiety and depression status. All the collected characteristics were entered into the multivariate logistic regression models, and only significant variables remained in the final models. Odds ratios and 95% CIs were calculated for each variable. Linear mixed models were used to calculate the influencing factors with the SAS score, SDS score and dimension score. SAS statistical software version 9.4 (SAS Institute Inc.) was used for statistical analysis. All statistical analyses were tested at a significance level of 0.05 (two-sides).

Results

Demographic characteristics of the enrolled health care workers and patients

A total of 203 health care workers assigned to isolation wards during the COVID-19 pandemic period from January to August were enrolled and completed the survey. The demographic characteristics of the enrolled FHWs are shown in Table 1. Across the three periods (national outbreak period, sporadic period, and local epidemic period), there was no significant difference among the medical staff assigned to the isolation wards in terms of age, with most staff being approximately 30 years old ($F = 0.724$, $P = 0.696$). The number of female workers was almost double the number of male workers ($P = 0.801$). The FHWs surveyed in the local epidemic period had lower education levels than those surveyed in the previous periods, with 34.41% of FHWs having a master's degree or higher vs. 54.10 and 57.14% in the national outbreak period and sporadic period, respectively ($P = 0.011$). The FHWs surveyed in different periods showed no significant differences regarding other demographic characteristics, including marital status, number of children in the participant's family, and area of residence. Notably, the workload differed significantly across the three periods and presented an upward trend. The doctor-patient ratio was only 0.75 during the national outbreak period and rose to 4.21 during the local epidemic period, which meant that medical resources were so limited that one doctor had to treat 4–5 patients in the isolation wards during the local epidemic period. A total of 206 SIPs in the isolation wards were enrolled and completed the survey. As shown in Table 1, the demographic characteristics of patients in the isolation wards were similar among patients surveyed during the national outbreak period, sporadic period and local epidemic period (all P-values > 0.05).

The psychological status of participants in the isolation ward during the COVID-19 pandemic

The psychological status of health care workers in the isolation wards was significantly poor during the local epidemic period (Table 2). The SAS and SDS scores and the scores for almost all the dimensions of the SAS/SDS, except for the second dimension of the SDS ($P = 0.09$), were higher in the local epidemic period than in the national outbreak and sporadic periods (all P-values < 0.001). The health care workers assigned to isolation wards during the local epidemic period had SAS and

TABLE 1 The demographic characteristics of enrolled health care workers and patients during the national outbreak period, sporadic period and local epidemic period.

	National outbreak period	Sporadic period	Local epidemic period	F/χ^2 value	*P*-value
FHWs	$n = 61$	$n = 49$	$n = 93$		
Age	31.30 ± 4.41	30.78 ± 4.24	31.83 ± 5.79	0.724	0.696
Sex					
Male	20 (32.79)	14 (28.57)	26 (27.96)	0.443	0.801
Female	41 (67.21)	35 (71.43)	67 (72.04)		
Area of residence					
Fengtai district	10 (16.39)	4 (8.16)	14 (15.05)	1.777	0.411
Other district	51 (83.61)	45 (91.84)	79 (84.95)		
Education level					
Bachelor's or below	28 (45.90)	21 (42.86)	61 (65.59)	9.093	0.011
Master's or above	33 (54.10)	28 (57.14)	32 (34.41)		
Marital status					
Not married	21 (34.43)	16 (32.65)	31 (33.33)	0.040	0.980
Married or divorced	40 (65.57)	33 (67.35)	62 (66.67)		
Children					
None	33 (54.10)	29 (59.18)	40 (43.01)	3.875	0.144
1 or more	28 (45.90)	20 (40.82)	53 (56.99)		
Doctor-patient ratio	0.75	1.37	4.21	202	<0.001
Patients	$n = 33$	$n = 35$	$n = 138$		
Age	38.09 ± 11.80	37.46 ± 12.00	39.92 ± 14.00	0.446	0.800
Sex					
Male	14 (42.42)	20 (57.14)	73 (52.90)	1.627	0.443
Female	19 (57.58)	15 (42.86)	65 (47.10)		
Area of residence					
Fengtai district	10 (30.30)	14 (40.00)	43 (31.16)	1.803	0.582
Other district	23 (69.70)	21 (60.00)	95 (68.84)		
Education level					
Bachelor's or below	29 (87.88)	27 (77.14)	127 (92.03)	#	0.060
Master's or above	4 (12.12)	8 (22.86)	11 (7.97)		
Marital status					
Not married	12 (36.36)	10 (28.57)	39 (28.26)	0.861	0.650
Married or divorced	21 (63.64)	25 (71.43)	99 (71.74)		
Children					
None	15 (45.45)	11 (31.43)	45 (32.61)	2.118	0.347
1 or more	18 (54.55)	24 (68.57)	93 (67.39)		

#Fisher's exact test. FHWs, Health care workers.

SDS scores of 44.14 ± 14.32 and 50.53 ± 13.36, respectively, which were 8–10 points higher than the scores in the national outbreak and sporadic periods (Figure 3A). Furthermore, the proportion of health care workers with anxiety (34.41%) and depression (41.94%) was higher during the local epidemic period ($P < 0.001$). The prevalence of anxiety and depression in FHWs during the national outbreak period and sporadic period was 1.6 and 13.1% and 6.1 and 8.1%, respectively. The overall incidence of anxiety and depression in FHWs was 17.7 and 25.1%, respectively.

The psychological status of the patients in the isolation wards was stable overall (Figure 3B) and showed no significant differences across the three periods (Table 2). The prevalence of anxiety and depression among the SIPs was 0 and 21% during the national outbreak period, 5.7 and 8.6% during the sporadic period, and 4.4 and 21.7% during the local epidemic period, respectively. The average incidence of anxiety and depression among the SIPs was 3.9 and 19.4%, respectively.

There were evident changes in health care workers' and patients' psychological status across the three periods (Figure 4). A comparison of the SAS and SDS scores of the patients in the isolation wards showed an approximately equilateral triangle indicating similar values in each period. In contrast to the patients, the health care workers in the isolation wards scored

TABLE 2 Depression and anxiety status and scores for the enrolled health care workers and patients.

	National outbreak period	Sporadic period	Local epidemic period	F/χ^2 value	*P*-value
FHWs	$n = 61$	$n = 49$	$n = 93$		
SAS scores	32.52 ± 6.08	34.59 ± 7.62	44.14 ± 14.32*	34.211	<0.001
1	60 (98.36)	46 (93.88)	61 (65.59)	33.084	<0.001
≥2	1 (1.64)	3 (6.12)	32 (34.41)		
F1	7.73 ± 1.75	8.06 ± 2.09	10.47 ± 4.29*	19.736	<0.001
F2	9.04 ± 2.87	9.49 ± 2.89	14.35 ± 4.90*	57.31	<0.001
F3	6.84 ± 0.98	7.53 ± 1.87	8.53 ± 3.08**	15.507	<0.001
F4	8.61 ± 2.36	9.13 ± 2.71	10.42 ± 3.88**	8.846	0.012
SDS scores	42.28 ± 10.06	42.51 ± 9.01	50.53 ± 13.36*	20.851	<0.001
1	53 (86.89)	45 (91.84)	54 (58.06)	26.142	<0.001
≥2	8 (13.11)	4 (8.16)	39 (41.94)		
D1	15.41 ± 4.80	15.48 ± 4.27	18.21 ± 5.62*	13.289	0.001
D2	10.64 ± 2.72	10.28 ± 2.86	11.37 ± 3.37	4.812	0.09
D3	5.29 ± 1.93	5.43 ± 1.68	7.06 ± 2.87*	19.391	<0.001
D4	5.49 ± 1.86	5.48 ± 1.80	7.50 ± 2.86*	27.354	<0.001
D5	5.10 ± 1.55	5.43 ± 1.26	6.01 ± 1.80**	11.648	0.003
SIPs	$n = 33$	$n = 35$	$n = 138$		
SAS scores	32.18 ± 7.18	31.29 ± 6.79	34.42 ± 8.83	4.969	0.083
1	33 (100.00)	33 (94.29)	132 (95.65)	#	0.490
≥2	0	2 (5.71)	6 (4.35)		
F1	7.73 ± 1.75	7.21 ± 1.69	8.36 ± 2.77	5.797	0.055
F2	9.85 ± 3.81	9.57 ± 3.05	10.73 ± 3.99	2.77	0.25
F3	6.63 ± 0.80	6.71 ± 1.64	7.03 ± 1.66	5.1	0.078
F4	7.65 ± 1.92	7.43 ± 1.71	7.93 ± 2.41	0.555	0.758
SDS scores	43.97 ± 10.80	39.69 ± 8.41	43.22 ± 11.39	2.611	0.271
1	26 (78.79)	32 (91.43)	108 (78.26)	3.175	0.205
≥2	7 (21.21)	3 (8.57)	30 (21.74)		
D1	17.20 ± 6.21	15.07 ± 3.59	16.98 ± 5.23	2.244	0.326
D2	10.30 ± 3.42	9.32 ± 3.57	9.69 ± 3.72	1.454	0.483
D3	5.76 ± 2.02	5.32 ± 2.21	5.59 ± 2.19	1.406	0.495
D4	4.85 ± 1.55	4.75 ± 1.24	5.54 ± 1.95	6.466	0.039
D5	5.49 ± 1.17	4.79 ± 1.41	5.01 ± 1.62	4.574	0.102

#Fisher's exact test. *The variables in the local epidemic period were significantly different from those in both the national outbreak period and the sporadic period. **The variables in the local epidemic period were significantly different from those in the national outbreak period. SAS: F1, anxiety and panic (items 1, 2, 3, 4, 18); F2, somatic control (items 5, 9, 13, 17, 19); F3, vestibular sensations (items 6, 10, 11, 12, 14); F4, gastrointestinal/muscular sensations (items 7, 8, 15, 16, 20). SDS: D1, core depressive factor (items 1, 3, 6, 14, 17, 18, 19, 20); D2, cognitive factor (items 10, 11, 12, 16); D3, anxiety factor (items 4, 13, 15); D4, somatic factor (items 5, 7, 9); D5, (items 2, 8).

much higher during the local epidemic period, with skewness in the triangle.

Comparison of the Zung self-rating anxiety scale and the Zung self-rating depression scale scores between frontline health care workers and suspected infected patients during the periods

Figure 5 and Table 2 show the differences between the scores of FHWs and SIPs during the COVID-19 pandemic. There was no significant difference between FHWs and SIPs during the national outbreak period ($P = 0.484$ and $P = 0.456$). In the sporadic period, the SAS scores of the FHWs (34.59 ± 7.62) were higher than those of the SIPs (31.29 ± 6.79), with a *p*-value of 0.014. There was no significant difference in SDS scores between FHWs and SIPs during the sporadic period ($P = 0.176$). In the local epidemic period, the SAS and SDS scores of the FHWs were both higher than those of the SIPs ($P < 0.001$).

The anxiety rate in FHWs was 17.7%, which was higher than that in SIPs (3.9%) ($\chi^2 = 20.430$, $P < 0.001$). The depression rates in SIPs and FHWs were 19.4 and 25.1%, respectively ($\chi^2 = 1.924$, $P = 0.165$).

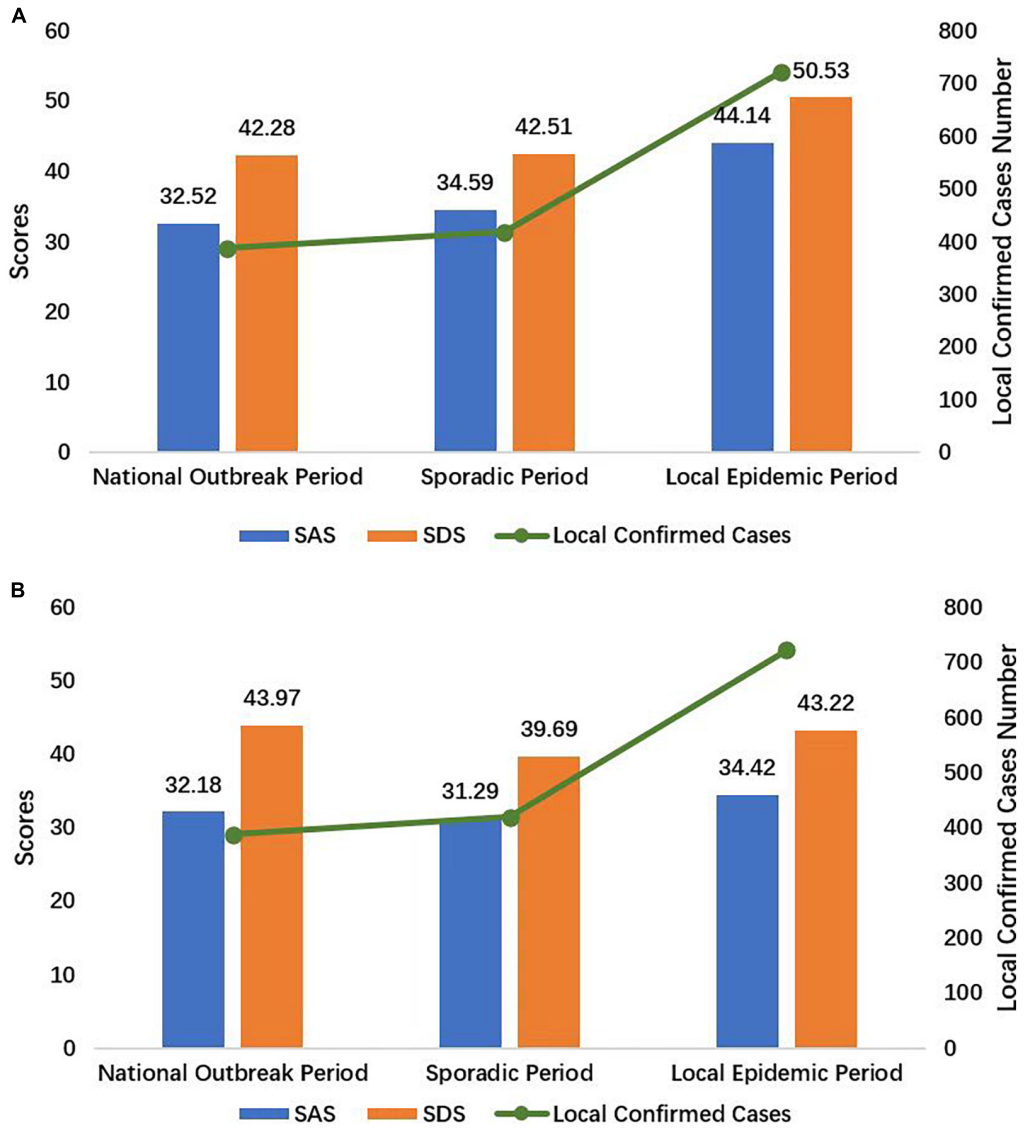

FIGURE 3
The SAS and SDS scores of FHWs **(A)** and SIPs **(B)** during the national outbreak, sporadic and local epidemic periods. *SAS*, the Zung Self-Rating Anxiety Scale; *SDS*, the Zung Self-Rating Depression Scale; FHWs, frontline health care workers; SIPs, suspected infected patients.

Factors influencing anxiety and depression among doctors in isolation wards during the COVID-19 pandemic

The multivariate logistic regression models (Table 3) showed that age ($OR = 0.248$, 95% CI: 0.068–0.905) and the doctor-patient ratio ($OR = 2.434$, 95% CI: 1.705–3.476) were independent factors of anxiety, while for depression, only the doctor–patient ratio was an independent factor ($OR = 1.718$, 95% CI: 1.369–2.156).

The linear mixed models (Table 4) showed that age influenced the total SAS ($P = 0.011$), total SDS ($P = 0.029$), F1 ($P = 0.007$), F2 ($P = 0.011$), F3 ($P = 0.026$), D1 ($P = 0.038$), and D4 ($P = 0.014$) scores. Sex also independently influenced the total SAS ($P = 0.030$), F2 ($P = 0.037$), F3 ($P = 0.040$), and F4 ($P = 0.049$) scores. The doctor-patient ratio independently influenced most of the dimension scores, including total SAS and SDS, F1, F2, F3, F4, D1, D3, D4, and D5 scores (all $P < 0.005$).

Discussion

A total of 409 participants were included in this study, including FHWs and patients from the isolation wards of Beijing Friendship Hospital in Beijing, China. Overall, the incidence

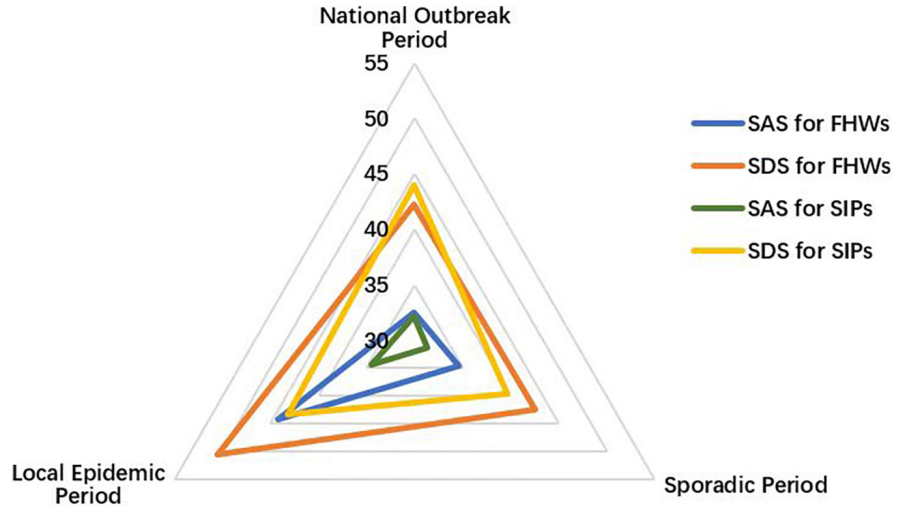

FIGURE 4
The SAS and SDS scores for frontline health care workers (FHWs) and suspected infected patients (SIPs). *SAS*, the Zung Self-Rating Anxiety Scale; *SDS*, the Zung Self-Rating Depression Scale.

of anxiety and depression among FHWs was 17.7 and 25.1%, respectively, which was significantly higher than the incidence among SIPs (3.9 and 19.4%). Furthermore, the occurrence of APDs in patients was basically stable during the three different periods, but the figures for FHWs fluctuated drastically across periods. The scores in the local epidemic period were significantly higher than those in the previous two periods. In addition, age, sex, and doctor-patient ratio were independent risk factors for APDs. It is worth noting that the doctor-patient ratio was the strongest influencing factor for almost all dimensions of the SAS and SDS (only the cognitive dimension in the SDS was not related).

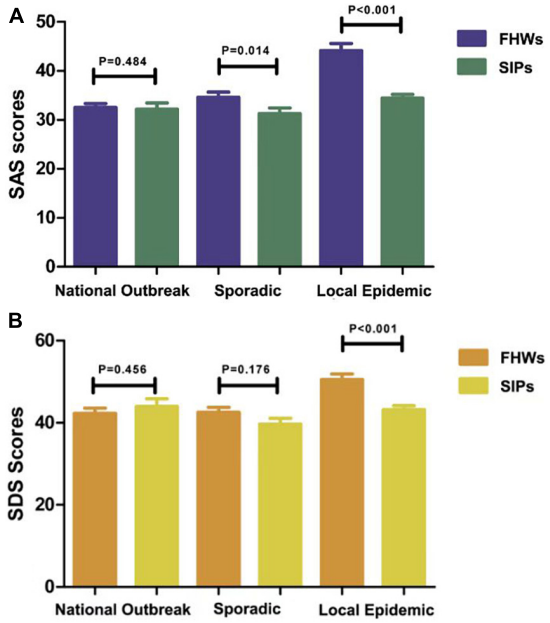

FIGURE 5
Comparison of SAS **(A)** and SDS **(B)** scores of frontline health care workers (FHWs) and suspected infected patients (SIPs) during different periods.

Theoretically, the closeness of contact with COVID-19 determines the risk of being infected and the degree of APD occurrence (22, 23). A recent study (24) based on 43 investigations showed that anxiety and depression were more frequent in FHWs than in non-FHWs. Previous studies (25) showed that anxiety and depression rates were 20.8 and 29.2%, respectively, in infected patients. Among FHWs, the anxiety and depression rates ranged from 38.5 to 44.6% and 21.7 to 50.4%, respectively (22, 26). In our study, the prevalence was consistent with previous studies. It was reported that the reasons for the higher prevalence of APD among FHWs were sociodemographic factors, current and past medical history, psychological and social factors, and job-related factors (24).

The brain is the central organ of stress adaptation that is responsible for sensing and judging the degree of stress and reacting accordingly physiologically and behaviorally (27). Acute and chronic stress can lead to imbalances in the neural circuits of cognition, anxiety and emotion, which in turn affect the physiology and behavior of the whole body through neuroendocrine, autonomic nerve, immune, and metabolic mediators (27, 28). Therefore, when the experience of tension and danger goes beyond the body's short-term adaptive capability, neural circuits become blocked, which results in mental disorders, such as schizophrenia, anxiety, and depression (28). This can explain why the occurrence of anxiety, depression and other psychological disorders was significantly higher

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TABLE 3 Factors influencing anxiety and depression status in univariate and multivariate logistic regression models.

	Univariate logistic regression model			Multivariate logistic regression model		
	OR	95% CI	*P*	OR	95% CI	*P*
Anxiety						
Age	0.384	0.111–1.330	0.131	0.248	0.068–0.905	0.035
Sex						
Male	Ref	Ref	Ref			
Female	2.389	0.938–6.084	0.068			
Area of residence						
Fengtai district	Ref	Ref	Ref			
Other district	0.99	0.349–2.807	0.985			
Education level						
Bachelor's degree or below	Ref	Ref	Ref			
Master's degree or above	0.531	0.249–1.131	0.101			
Marital status						
Not married	Ref	Ref	Ref			
Married or divorced	0.751	0.357–1.581	0.451			
Children						
None	Ref	Ref	Ref			
1 or more	1.012	0.492–2.080	0.974			
Doctor-patient ratio	2.338	1.644–3.326	<0.001	2.434	1.705–3.476	<0.001
Depression						
Age	0.287–1.728	0.444				
Sex						
Male	Ref	Ref	Ref			
Female	1.009	0.503–2.024	0.979			
Area of residence						
Fengtai district	Ref	Ref	Ref			
Other district	0.814	0.335–1.982	0.651			
Education level						
Bachelor's degree or below	Ref	Ref	Ref			
Master's degree or above	0.962	0.509–1.820	0.906			
Marital status						
Not married	Ref	Ref	Ref			
Married or divorced	1.285	0.645–2.558	0.476			
Children						
None	Ref	Ref	Ref			
1 or more	1.63	0.857–3.098	0.136			
Doctor-patient ratio	1.718	1.369–2.156	<0.001	1.718	1.369–2.156	<0.001

OR: odds ratio.

among FHWs than among SIPs and other groups. FHWs were continuously exposed to health-damaging circumstances (29), while SIPs could be discharged after a short stay in the hospital when they tested negative.

In the present study, we found that the doctor-patient ratio was the strongest risk factor influencing the occurrence of APDs among FHWs by affecting various dimensions of the SAS and SDS, including anxiety and panic, somatic control, vestibular sensations, gastrointestinal/muscular sensation factors, core depression, anxiety, and somatic factors (20, 21). A higher doctor-patient ratio implied that FHWs had to care for and manage more patients. In addition, the high proportion of older individuals among SIPs meant that FHWs wearing protective clothing had to be more careful and perform more communication, medical documentation and complex treatments. Simultaneously, the increasing number of SIPs led to higher working hours and workload, causing FHWs to suffer higher psychological and physical pressures (30–33).

TABLE 4 Influencing factors in SAS scores, SDS scores, and dimension scores in the linear mixed model.

		Mixed model	
		β	*P*
SAS	Age	−0.475	0.011
	Sex	4.129	0.030
	Doctor-patient ratio	3.480	<0.001
F1	Age	−0.149	0.007
	Doctor-patient ratio	0.858	<0.001
F2	Age	−0.172	0.011
	Sex	1.434	0.037
	Doctor-patient ratio	1.615	<0.001
F3	Age	−0.090	0.026
	Sex	0.844	0.040
	Doctor-patient ratio	0.469	<0.001
F4	Sex	1.123	0.049
	Doctor-patient ratio	0.527	<0.001
SDS	Age	−0.436	0.029
	Doctor-patient ratio	2.732	<0.001
D1	Age	−0.182	0.038
	Education level	1.718	0.043
	Doctor-patient ratio	1.014	<0.001
D2	NA	NA	NA
D3	Doctor-patient ratio	0.546	<0.001
D4	Age	−0.100	0.014
	Doctor-patient ratio	0.631	<0.001
D5	Area of residence	−0.740	0.025
	Doctor-patient ratio	0.236	0.001

SAS: F1, anxiety and panic (items 1, 2, 3, 4, 18); F2, somatic control (items 5, 9, 13, 17, 19); F3, vestibular sensations (items 6, 10, 11, 12, 14); F4, gastrointestinal/muscular sensations (items 7, 8, 15, 16, 20). SDS: D1, core depressive factor (items 1, 3, 6, 14, 17, 18, 19, 20); D2, cognitive factor (items 10, 11, 12, 16); D3, anxiety factor (items 4, 13, 15); D4, somatic factor (items 5, 7, 9); D5, (items 2, 8); NA, not applicable.

In the early periods of COVID-19, Chinese government and hospitals took effective measures to address mental health problems, for example, adopting the psychological protection measures provided by the International Guidelines for Psychological Crisis Intervention, establishing psychological expert groups in hospitals and creating network mental health consulting services (6). Necessary training regarding professional knowledge, mental health, and protective equipment can build the confidence of health care workers, help them overcome the panic linked to the pandemic, and reduce nosocomial infections, thus reducing the occurrence of APDs (23). Above all, the findings suggest that in the long-term fight against COVID-19, more attention should be given to the workload of FHWs, including the doctor-patient ratio, working hours, and night duty arrangements. In addition, the establishment of critical care isolation wards is particularly important.

One strength of this study is that it tracked the dynamic changes in mental health status among participants in different periods. As a result, it provided objective and reliable results regarding the mental health impacts of the COVID-19 pandemic. A self-rating scale, the Zung Self-Rating Anxiety/Depression Scale (SAS/SDS), was adopted in this study. In addition, an in-depth dimensional analysis was conducted to show the main symptoms of anxiety and depression. However, several limitations exist in this study. First, the mental changes experienced by FHWs before and after isolation could not be followed up on due to the cross-sectional survey design of this study. Second, the convenience sampling methods and limited sample size might lead to selection bias. Third, the SAS and SDS have no diagnostic efficacy, even though they have been used in many psychological studies worldwide.

Conclusion

The present study reveals that FHWs have a much higher chance of experiencing APDs than do SIPs. Furthermore, the prevalence of anxiety and depression among SIPs remained relatively stable, while the prevalence among FHWs fluctuated drastically, with the highest incidence of anxiety and depression occurring during the local epidemic period. Analysis of the related risk factors proved that age, sex, and especially the doctor–patient ratio were independent risk factors for APDs. Our findings suggest that psychological assistance measures should be implemented not only in the anti-epidemic period but also before and after exposure to COVID-19. In addition, more concern and attention should be given to the workload of FHWs.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Beijing Friendship Hospital (2020-P2-161-01). The patients/participants provided their written informed consent to participate in this study.

Author contributions

YT and QZ collected the questionnaires and clinical data. QZ analyzed the data. YT and XD wrote the manuscript with input from all authors. XD and YC designed the study and reviewed the final manuscript. All authors

participated in designing various parts of the study and the interpretation of the results.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The changes in psychological symptoms of COVID-19 patients after "re-positive"

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Background: Previous studies have showed that individuals infected with COVID-19 were more likely to report psychological symptoms. However, little is known about the changes from testing positive to negative to positive again.

Methods: This survey was conducted through the questionnaires including the 7-item Generalized Anxiety Disorder (GAD-7), the 9-item Patient Health Questionnaire (PHQ-9), as well as the Self-Rating Scale of Sleep (SRSS) to explore the psychological status of COVID-19 and re-positive cases. "re-positive" is defined as a positive RT-PCR test at any time during the recovery period after testing negative.

Results: A total of 94 COVID-19 patients presented the prevalence rates of anxiety, depression, insomnia, and any of the three psychological symptoms being 26.6, 8.6, 12.8, and 31.9%, respectively. Among these, 32 cases were re-tested positive during the recovery period, with the prevalence rates of anxiety, depression, insomnia, and any of the three psychological symptoms being 21.9, 18.7, 31.2, and 37.5%, respectively. The psychological status after re-positive showed a significant decrease in anxiety ($P = 0.023$), an increase in depression, and a significant rise in insomnia ($P = 0.035$). For those with no psychological symptoms during initial-positive, after re-positive, 5.88% reported anxiety, 5.88% reported depression, and 11.76% reported insomnia. For those who experienced only anxiety symptoms during initial-positive, after re-positive, 33.3% reported depression, and 33.3% reported insomnia.

Conclusions: Our findings encompassed the urgent concern for anxiety in initial-positive COVID-19 patients, depression in re-positive COVID-19 patients, and insomnia in both initial and re-positive patients, hence enabling targeted interventions for appeasing the psychological burden of COVID-19 patients.

KEYWORDS

COVID-19 patients, re-positive, anxiety, depression, insomnia

Introduction

There is growing evidence of studies associating COVID-19 survivors with increased psychological symptoms. It's reported that symptoms aroused by COVID-19 infection, side effects of treatment, concerns about sequelae, social isolation, and stigma all partook to a higher risk of psychological symptoms in COVID-19 patients (1–3). Previous studies recounted that the prevalence of cases with post-infection anxiety ranges from 6.5 to 63% (4–6). In studies implicating both hospitalized and non-hospitalized patients, the prevalence rates for depression and insomnia range between 12 and 48 and 2–63%, respectively (4, 7, 8). Psychological symptoms and implications related to a COVID-19 infection comprise both acute and long-term consequences. In addition, the re-positive rate was found to be correlated to illness severity, according to the Acute Physiology and Chronic Health Evaluation II (APACHE II) severity-of-disease classification system, and the confusion, urea, respiratory rate, and blood pressure (CURB-65) score. Since the physical condition may worsen after re-positive, what will take place in the psychological status of COVID-19 patients remain unknown. This study aims to explore changes in the severity of psychological symptoms and the mutual changes in anxiety, depression, and insomnia in re-positive COVID-19 patients.

Methods

Participants and procedure

A total of 94 initially confirmed COVID-19 patients were enrolled from Bayan County and Pingfang District of Harbin City, in Heilongjiang Province from September 23, 2021, to December 31, 2021. Located in the northern part of Northeast China, Harbin is the capital city of Heilongjiang Province with a resident population of approximately 9.8 million. Since the outbreak of the COVID-19 pandemic in 2020, Harbin has been a low-prevalence city with two small-scale indigenous outbreaks.

These patients were diagnosed and treated fulfilling the criteria of the 8th version of the Guidelines on the Diagnosis and Treatment of COVID-19 by the National Health Commission of China. Confirmed patients with COVID-19 were treated at one of the designated hospitals, the Harbin Infectious Diseases Hospital, which was a dedicated hospital for COVID-19 patients. Once the RT-PCR test turned negative after the treatment, patients were transferred to designated Harbin Second Hospital for rehabilitation. Paper-and-pencil questionnaires were utilized to investigate the psychological symptoms of all COVID-19 patients transferred to Harbin Second Hospital. A total of 94 respondents were enrolled except for two children. "Re-positive" is interpreted as a positive RT-PCR test at any time during the 14 days or 14+7 days recovery period in the Harbin Second Hospital. Of the 94 COVID-19 negative cases, 32 were re-positive during the recovery period. The re-positive patients will be re-transferred to Harbin Infectious Diseases Hospital for treatment until their tests turn negative and then transferred back to Harbin Second Hospital for recovery. Both the initial-positive patients and re-positive patients were surveyed within 2 days of admission to the Harbin Second Hospital. All the 32 re-positive cases received the two questionnaires at intervals of more than 2 weeks. This study was approved by the Research Ethics Committee of the First Affiliated Hospital of Nanchang University (Ethical number: 2020-051).

Measures

Anxiety, depressive symptoms, and insomnia were assessed using the 7-item Generalized Anxiety Disorder (GAD-7) (9), the 9-item Patient Health Questionnaire (PHQ-9) (10), and the Self-Rating Scale of Sleep (SRSS) (11) in Chinese version, separately. Each item on the GAD-7 and PHQ-9 was gauged with a four-point Likert scale (0= "not at all" to 3 = "extremely") to infer the severity of a particular symptom within the past 2 weeks. There are 10 items in total, and each item has five levels (1–5). The higher the score, the more severe the sleep problem. The cut-offs to screen for possible positive cases of anxiety, depression and sleep disorders were a GAD-7 score $\geq$5, a PHQ-9 score $\geq$5, and an SRSS score $\geq$23, respectively. The Cronbach's α for self-reported GAD-7, PHQ-9, and SRSS for COVID-19 patients in the first investigation were 0.92, 0.78, and 0.91, respectively. For COVID-19 re-positive patients in the second survey, the Cronbach's α for GAD-7, PHQ-9, and SRSS were 0.96, 0.84, and 0.92, respectively.

Statistical analyses

Descriptive analyses were executed based on frequencies for all variables, including demographic data, as well as factors linked with the risk of COVID-19 cases, which were applied by the exact probability tests as the low frequencies. The paired samples *t*-test or Chi-squared test was conducted to spot the differences in psychological status of the 32 patients pre-and post-re-positive. Data were analyzed employing the statistical software IBM SPSS version 22 (SPSS Inc., Chicago, IL, USA), and figures were drawn by GraphPad prism 9 (GraphPad Software, Inc., San Diego, CA). All statistical analysis was performed with a *P*-value $<$0.05 using a two-tailed test deemed statistically significant.

Results

Sociodemographic characteristics

A total of 94 initially confirmed COVID-19 patients were implicated, with 55 females and 39 males, of which 32 were re-tested positive for COVID-19 during rehabilitation. The sociodemographic characteristics of 94 patients were as follows: 58.5% female, 50.0% older than the age of 45 years, 16.0% with at least one underlying disease, 84.0% quarantined for more than 15 days, 76.6% married, 83.0% with high school or less, 24.4% with no source of revenue.

The prevalence rates of anxiety, depression, and insomnia symptoms among COVID-19 patients

The prevalence of anxiety, depression, insomnia, and any of the three psychological symptoms in initially confirmed 94 COVID-19 patients were 26.6, 8.6, 12.8, and 31.9% (see Table 1), respectively. For the 32 re-positive cases, the prevalence rates were 43.8, 12.5, 21.9, and 46.9% (data not shown) in the initial-positive, respectively. The prevalence rates after re-positive were 21.9, 18.7, 31.2, and 37.5 %, with increases of −50.0% ($\chi^2 = 6.411$, $P = 0.001$), 50.0% ($\chi^2 = 0.117$, $P = 0.732$), 42.9% ($\chi^2 = 6.733$, $P = 0.009$) and −20.0% ($\chi^2 = 16.737$, $P < 0.001$). Most of the initial COVID-19 cases screening positive for anxiety, depression, and insomnia showed mild symptoms. Nevertheless, there was an increase in the proportion of cases with severe anxiety and moderate insomnia in COVID-19 patients after re-positive. Notably, an impressive proportion of COVID-19 patients with anxiety symptoms was observed in cases with medical history than those without ($P < 0.05$) (see Table 2). Moreover, a higher proportion of re-positive patients with insomnia was viewed over the age of 45 years ($P < 0.05$) (see Table 3). We also compared the demographic characteristics of 32 re-positive cases and the remaining 62 cases without re-positive cases and found that there was no statistical difference in demographic characteristics between the two groups except that the proportion of cases with a medical history was higher in re-positive cases than that in the other group (P=0.006) (see Supplementary Table 1).

The severity changes of the three psychological symptoms after re-positive

Furthermore, the paired samples t-test comparing the consistency assessment of COVID-19's severity between 32 initial-positive and re-positive, reflected a general decrease in anxiety ($P = 0.023$), with most of the re-positive patients who initially exhibited mild or moderate anxiety symptoms becoming normal (Figure 1A); with a slight but not significant increase in depression symptoms ($P = 0.949$), 66.67% of initially mild and 100.00% of initially moderately cases altering into normal, while 17.85% of initially normal cases presented with depression (Figure 1B). Moreover, these patients withstood a significant increase in insomnia after re-positive ($P = 0.035$), as 20.00% of initially normal patients suffered from insomnia and 14.29% of initially mild insomnia transformed into the moderate level (Figure 1C).

The mutual changes of three psychological symptoms after re-positive

In addition, we compared the conversion rates among the three psychological symptoms between initial-positive and re-positive. Results demonstrated that for those who had no psychological symptoms during initial-positive, after re-positive, 5.88% reported anxiety problems, 5.88% reported depression symptoms, and 11.76% reported insomnia. For those who were only positive for anxiety symptoms during initial-positive, after re-positive, 33.3% reported depression, and 33.3% reported insomnia (see Table 4).

Discussion

In this study, we analyzed the psychological effects of the re-positive test on COVID-19 patients by comparing the changes in psychological symptoms between the initial-positive and re-positive. The detection rate of cases with psychological symptoms in this study was slightly lower than those announced in previous studies. A study from the late COVID-19 implied that the prevalence of depression and anxiety symptoms was 49.06 and 56.60% in COVID-19 patients (12). Additionally, a meta-analysis of 31 studies of COVID-19 patients revealed a pooled prevalence of 47% for anxiety, 45% for depression, and 34% for insomnia (8). The differences may be pertained to the epidemic control during the study period, the progress of vaccine development and vaccination, COVID-19 treatment, measurement, and the severity of the included subjects. Since these studies were performed at the early stages of the outbreak, when little was known about the virus, an effective vaccine, or a specific therapeutic agent, the uncertainty bestowed to high-level patient stress and fear of disease. Furthermore, the information overload generated by constant news media reports about deaths of infected cases contributed to patients' vulnerability to depression, and even negative thoughts after infection (13).

TABLE 1 The prevalence and severity of anxiety, depression, and insomnia among COVID-19 patients.

	Anxiety		Depression		Insomnia		Anyone[†]	
	COVID-19 cases ($N = 94$) *n* (%)	Re-positive cases ($N = 32$) *n* (%)	COVID-19 cases ($N = 94$) *n* (%)	Re-positive cases ($N = 32$) *n* (%)	COVID-19 cases ($N = 94$) *n* (%)	Re-positive cases ($N = 32$) *n* (%)	COVID-19 cases ($N = 94$) *n* (%)	Re-positive cases ($N = 32$) *n* (%)
Normal	69 (73.4%)	25 (78.1%)	86 (91.4%)	26 (81.3%)	82 (87.2%)	22 (68.8%)	64 (68.1%)	20 (62.5%)
Mild	20 (21.3%)	3 (9.4%)	6 (6.4%)	4 (12.5%)	12 (12.8%)	8 (25.0%)	29 (30.9%)	10 (32.3%)
Moderate	3 (3.2%)	1 (3.1%)	1 (1.1%)	1 (3.1%)	0	2 (6.2%)	4 (4.3%)	3 (9.4%)
Severe	2 (2.1%)	3 (9.4%)	1 (1.1%)	1 (3.1%)	0	0	3 (3.2%)	3 (9.4%)

[†] The total rate is more than 100.0% since comorbidity is indicated here.

TABLE 2 The demographic distribution of psychological symptoms among initially confirmed COVID-19 patients ($N = 94$).

Characteristics	Group	Anxiety		Depression		Insomnia	
		N (%)	*P*	*N* (%)	*P*	*N* (%)	*P*
Gender	Male	8 (20.5%)	0.345	1 (2.6%)	0.134	3 (7.7%)	0.348
	Female	17 (30.9%)		7 (12.7%)		9 (16.4%)	
Age	<45	7 (14.9%)	0.065	3 (6.4%)	0.714	4 (8.5%)	0.355
	≥45	18 (38.3%)		5 (10.6%)		8 (17.0%)	
Medical history	No	17 (21.5%)	0.022	5 (6.3%)	0.113	8 (10.1%)	0.096
	Yes	8 (53.3%)		3 (20.0%)		4 (26.7%)	
The total duration of isolation, day	7–15	6 (40.0%)	0.125	2 (13.3%)	0.609	1 (6.7%)	0.683
	>15	19 (24.1%)		6 (7.6%)		11 (13.9%)	
Marital status	Married	20 (27.8%)	0.786	4 (5.6%)	0.084	8 (11.1%)	0.466
	Others	5 (22.7%)		4 (18.1%)		4 (18.1%)	
Educational level	High school or less	22 (28.2%)	0.546	7 (9.0%)	1.000	10 (12.8%)	1.000
	Undergraduate degree/college	3 (18.8%)		1 (6.3%)		2 (12.5%)	
Source of income	No	3 (13.0%)	0.217	0 (0)	0.276	3 (13.0%)	0.901
	Not sure	3 (25.0%)		1 (8.3%)		2 (16.7%)	
	Yes	19 (32.2%)		7 (11.9%)		7 (11.9%)	

The stressors for COVID-19 patients were the disease itself, treatment regimen, and worries about family health, resulting in changes in mood, sleep, behavior, etc. The gradual adaptation process was reflected in COVID-19 patients' attitudes upon admission, from uncertainty about the disease to anticipation and suspicion of the examinations, to confrontation and acceptance following the diagnosis, which ultimately culminated in gratitude for the experience (14). This study also identified a significant reduction in symptom burden associated with depression and anxiety over time with hospitalization (15). However, cases who had been gradually improving physically and psychologically with the treatment appeared to experience changes in their psychological state after experiencing a re-positive result. Our findings indicated a general decrease in anxiety symptoms, and a slight increase in depressive symptoms of COVID-19 patients after re-positive. Notably, the sleep status of the patients deteriorated considerably, with a significant increase in insomnia. This might be explained by the disrupted discharge expectations and psychological distress caused by all kinds of uncertainties after re-positive.

For re-positive COVID-19 cases, the considerable worsening of insomnia earned attention. Being in prolonged hospitalization, their sleep habits might be affected by reduced physical activity, psychological stress, lack of a regular work schedule and social activities, changes in living conditions, etc. (16). Furthermore, due to the absence of other recreational pastimes and a rigorous schedule, COVID-19 patients might

TABLE 3 The demographic distribution of psychological symptoms among re-positive confirmed COVID-19 patients ($N = 32$).

Characteristics	Group	Anxiety		Depression		Insomnia	
		N (%)	*P*	*N* (%)	*P*	*N* (%)	*P*
Gender	Male	3 (30.0%)	0.648	3 (30.0%)	0.346	4 (40.0%)	0.683
	Female	4 (18.2%)		3 (13.6%)		6 (27.3%)	
Age	<45	1 (8.3%)	0.212	1 (8.3%)	0.370	0(0)	0.004
	≥45	6 (30.0%)		5 (25.0%)		10 (50.0%)	
Medical history	No	5 (22.7%)	1.000	4 (18.2%)	1.000	6 (27.3%)	0.683
	Yes	2 (20.0%)		2 (20.0%)		4 (40.0%)	
The total duration of isolation, day	7–15	N/A	N/A	N/A	N/A	N/A	N/A
	>15	7 (21.9%)		7/32(21.9%)		10 (31.25%)	
Marital status	Married	6 (25.0%)	0.646	5 (20.8%)	1.000	8 (33.3%)	1.000
	Others	1 (12.5%)		1 (12.5%)		2 (25.0%)	
Educational level	High school or less	7 (25.9%)	0.560	6 (22.2%)	0.555	9 (33.3%)	1.000
	Undergraduate degree/college	0(0)		0 (0)		1 (20.0%)	
Source of income	No	1 (14.3%)	1.000	1 (14.3%)	1.000	2 (28.6%)	1.000
	Not sure	0 (0)		0 (0)		1 (50.0%)	
	Yes	6 (26.1%)		5 (21.7%)		7 (30.4%)	

also devour more time on electronic devices and have particular potential to experience altered biorhythms with late bedtimes and late wakeups during hospital admission (17). Previous research has also reported that spending more time on electronic devices before falling asleep affects sleep quality (18). In addition, re-positive patients are likely to be more apprehensive about their health status and experience greater fear of sequelae. With extended treatment periods, there may also be a feeling of more loneliness. These presumably explain the deterioration of sleep status in re-positive patients. The social and family burden of cases over 45 years old were relatively heavy, and the problem of insomnia in this group after re-positive was more prominent as shown in this study. Besides, our study also unearthed a slight increase in overall depression in re-positive patients, with some rated as normal or anxiety symptoms at initial-positive suffering from depression symptoms after re-positive. This result is consistent with previous studies in Wuhan (19). Patients receiving the RT-PCR re-positive result probably tend to suffer helplessness, worry, and disappointment, which facilitates the co-morbidity of anxiety symptoms and depression symptoms.

During the COVID-19 pandemic, health concerns are associated with clinically significant levels of psychological problems. WHO noted an increased risk of serious illness due to COVID-19 in patients with pre-existing non-communicable diseases, comprising cardiovascular disease, diabetes, cancer, etc. (20). Meanwhile, comorbid chronic disease has been identified as the most important risk factor for COVID-19 death (21), and some diseases such as myasthenia gravis may be exacerbated due to COVID-19 infection (22). Similar to previous studies (23–25), patients with other prior medical conditions were more likely to have anxiety symptoms. Besides, a significantly higher percentage of patients with a medical history in the re-positive group was also observed. These results may be attributed to the possibility that patients with medical history are more worried about their health status and fear and uncertainty about the physical impact of the interaction between the underlying disease and COVID-19 infection. Moreover, this distress and concern of patients with medical history may be aggravated after re-positive, triggering varying degrees of insomnia. Findings imply the significance of psychological interventions to address the heightened risk of depression and insomnia in re-positive COVID-19 patients.

This study had several impediments. First, the results of this study were limited to a sample of COVID-19 patients with non-severe disease types. Next, we employed a self-assessment scale, which may lead to recall bias. The current study points up the critical importance of screening and monitoring the psychological symptoms of re-positive COVID-19 patients and offering necessary psychological support and

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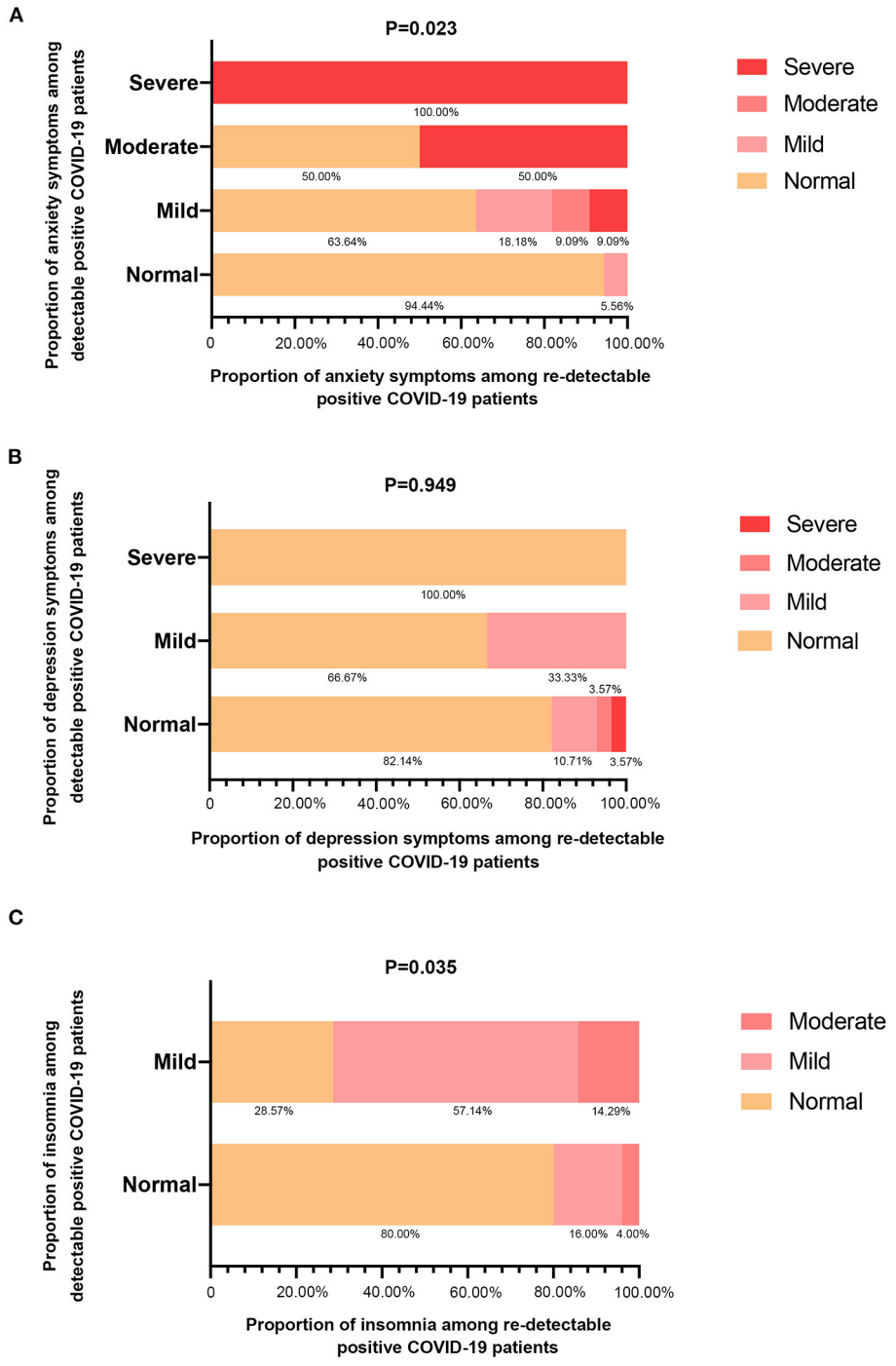

FIGURE 1
Stacked bar charts illustrated the conversion of psychological status after re-detectable positive for COVID-19 patients following anxiety symptoms **(A)**, depression symptoms **(B)**, and insomnia **(C)**. Statistical comparison was obtained by the paired samples *t*-test for the alteration levels of all mental health problems.

intervention. In this process, special attention should be paid to the anxiety symptoms of initial-positive COVID-19 patients, depression in re-positive COVID-19 patients, and insomnia symptoms of both initial and re-positive patients, to lessen the psychological burden of patients with COVID-19.

TABLE 4 The mutual changes of psychological symptoms after re-positive.

Initial-positive cases	Total	Re-positive cases		
		Anxiety + *N* (%)	Depression + *N* (%)	Insomnia + *N* (%)
Anxiety-, Depression-, Insomnia-	17	1 (5.88%)	1(5.88%)	2 (11.76%)
Anxiety+, Depression -, Insomnia-	6	3 (50.00%)	2 (33.33%)	2 (33.33%)
Anxiety -, Depression +, Insomnia-	0	N/A	N/A	N/A
Anxiety -, Depression -, Insomnia+	1	0 (0)	0 (0)	1 (100.00%)

(+) self-report positive, (-) self-report negative.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

This study was approved by the Research Ethics Committee of the First Affiliated Hospital of Nanchang University (Ethical number: 2020-051). The patients/participants provided their written informed consent to participate in this study.

Author contributions

ML planned the study. XW and QF were involved in the data collection and curation process. HC performed the data processing. YH and TG analyzed the results and interpreted them. YL and JX drafted the original manuscript. HC and ML implemented major revisions to the manuscript and ultimately approved the manuscript for publication. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.1010004/full#supplementary-material

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The relations between different components of intolerance of uncertainty and symptoms of depression during the COVID-19 pandemic: A network analysis

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Background: The relations between depression and intolerance of uncertainty (IU) have been extensively investigated during the COVID-19 pandemic. However, there is a lack of understanding on how each component of IU may differentially affect depression symptoms and vice versa. The current study used a network approach to reveal the component-to-symptom interplay between IU and depression and identify intervention targets for depression during the COVID-19 pandemic.

Methods: A total of 624 college students participated in the current study. An IU-Depression network was estimated using items from the 12-item Intolerance of Uncertainty Scale and the Patient Health Questionnaire-9. We examined the network structure, node centrality, and node bridge centrality to identify component-to-symptom pathways, central nodes, and bridge nodes within the IU-Depression network.

Results: Several distinct pathways (e.g., "Frustration when facing uncertainty" and "Feelings of worthlessness") emerged between IU and Depression. "Fatigue" and "Frustration when facing uncertainty" were identified as the central nodes in the estimated network. "Frustration when facing uncertainty," "Psychomotor agitation/retardation," and "Depressed or sad mood" were identified as bridging nodes between the IU and Depression communities.

Conclusion: By delineating specific pathways between IU and depression and highlighting the influential role of "Frustration when facing uncertainty" in maintaining the IU-Depression co-occurrence, current findings may inform

targeted prevention and interventions for depression during the COVID-19 pandemic.

KEYWORDS

COVID-19, depression, intolerance of uncertainty, network analysis, central nodes, bridge nodes

Introduction

The COVID-19 pandemic has developed into a global public health emergency (1). The pandemic has brought serious psychosocial stressors (e.g., lockdowns, keeping social distance, loss of livelihood, and decreases in economic activity), which could be dangerous for public mental health (2, 3). Specifically, these stressors may drive risks for the onset and development of depression symptoms (4). A recent meta-analysis found that depression was prevalent during the COVID-19 pandemic, with a prevalence rate of 33.7% (5). Owing to the COVID-19 pandemic, the global prevalence of the major depressive disorder has increased by about 27.6% (6). The COVID-19 pandemic has led to significant uncertainty for the general public (7). The detrimental effects of pandemic-related uncertainties may be particularly relevant to individuals with high levels of intolerance of uncertainty (IU), who are prone to present negative cognitions, emotions, and behaviors when facing unpredictable events (8, 9). This mental health inequality is well-documented in the literature, with IU being consistently identified as a predictor of depression severity during the COVID-19 pandemic (7, 10–12).

Despite the robust associations between IU and depression (9), there are limited insights into how specific components of IU are related to individual depression symptoms. Specifically, prior research tends to use the latent variable approach when estimating the relationships between IU and depression. The approach treated both IU and depression as unitary constructs (indexed by sum scores of IU instruments and depression instruments) and either compared differences in IU between depressed and non-depressed groups (based on the cut-off value of depression symptom sum scores) or examined IU in relation to depression severity (7, 9–12). Concerns have been raised over treating IU and depression as unitary constructs. Specifically, depression is a heterogeneous syndrome consisting of various symptoms (e.g., fatigue, sad mood, and appetite changes), which differ from each other in important domains [e.g., predisposing factors, (13, 14)]. Individual depression symptoms have shown different connections with insomnia (15), internet addictions (16), traumatic stress (17), abuse (18), negative life events (19), and emotion regulation difficulties (20, 21). Similarly, the heterogeneity of components that constitute IU has been observed in previous studies (22, 23). And individual IU components have shown different connections with different symptoms of anxiety (24) and problematic smartphone use (25). Hence, treating IU and depression as unitary constructs (using sum scores) may overlook their relationships at the component-to-symptom level, hindering conceptual understanding of mechanisms underlying the co-occurrence of IU and depression.

To address the aforementioned concerns, the current study adopted the network approach to explain the co-occurrence of IU and depression. From a network perspective, psychopathology may be viewed as a network consisting of interacting variables (nodes) and pathways (edges) among them (26, 27). Components of IU and symptoms of depression may directly interact with one another (*via* distinct symptom pathways) and result in the co-occurrence of IU and depression. By inspecting the network structure, researchers may delineate specific pathways through which constructs interact and reinforce each other. Further, network analysis provides novel indices to understand the role played by each node within the network (28). For instance, nodes with high "expected influence" are highly connected to the remaining nodes within the network, thus, may serve to maintain the network. Meanwhile, "bridge expected influence" quantifies nodes' cross-construct connectivity. Thus, nodes with high "bridge expected influence" are considered the key to the maintenance of co-occurrence (29).

To our knowledge, no study to date has examined how individual IU components may contribute to specific depression symptoms. To address this gap and extend previous research on the IU-Depression association, the current study modeled the component-to-symptom relationships between IU and depression *via* the network approach. In the present study, we incorporated different components of IU and symptoms of depression into one network. This study had three goals: (1) elucidate component-to-symptom pathways between IU and depression, (2) identify central nodes within the IU-Depression network, and (3) identify influential bridge nodes connecting IU and depression communities.

Methods

Study population and survey design

Due to the COVID-19 outbreak, we conducted this online survey between 16 and 18 December 2020 *via* Wenjuanxing (www.wjx.cn). A WeChat (one of the largest instant messaging applications in China) message with links to the online survey

was sent to all participants. Permission was gathered before the survey even began. The study only accepted participants who gave their consent. In the present network, we need to estimate 21 nodes (i.e., 12 components of IU and nine symptoms of depression) and 210 possible edges (i.e., each node has a connection with all other nodes). Although there are no definite guidelines yet as to how many participants we need per parameter, a rule of thumb put forward was the number of participants needed typically exceeds the possible parameters (30). Thus, the present network may need to recruit at least 231 participants. A total of 633 university students from Xijing University participated in our study. All of these participants were Chinese-speaking undergraduate students. Nine questionnaires were excluded due to their demographic information being incomplete. Finally, 624 questionnaires in all were collected. The First Affiliated Hospital of the Fourth Military Medical University's Ethics Committee authorized both this study and the format of the online survey (Project No. BWS16J012). The final sample consisted of 624 participants [57% female, mean age = 19.38, standard deviation (SD) = 1.12, range = 18–25 years].

Measures

Symptoms of depression

The Patient Health Questionnaire-9 (PHQ-9) is a self-assessment scale assessing depression symptoms over the past 2 weeks (31). This scale includes nine symptoms based on the diagnosis of DSM-IV depressive disorders and is widely used as a screening tool for clinical practice and research (31). Each item had responses ranging from 0 (not at all) to 3 (nearly every day). The PHQ-9 has been well-validated in Chinese college students (32). The scale showed good reliability in the current study (Cronbach's $\alpha = 0.89$).

Components of IU

The 12-item Intolerance of Uncertainty Scale (IUS-12) is a short, efficient scale for assessing IU (33). This scale measures a variety of uncertainty-related beliefs, emotions, and behaviors, such as "Frustration when facing uncertainty" and "Smallest doubt can stop me from acting" (33). Responses to each item ranged from 1 ("not at all characteristic of me") to 5 ("entirely characteristic of me"). In the present study, the Chinese version of IUS-12 was used to assess different components of IU (34). The Chinese version of IUS-12 has good reliability and validity. The scale used in the current study demonstrated good reliability (Cronbach's $\alpha = 0.84$).

Network analysis

The IU-Depression network was estimated using the Gaussian graphical model (GGM) (35). The GGM was estimated on the basis of non-parametric Spearman rho correlation matrices (36, 37). Within a GGM, the edge represents the partial correlation between nodes after controlling for all other nodes in the network (36). By using the graphical LASSO (Least Absolute Shrinkage and Selection Operator) algorithm, a regularized GGM was obtained (38). In this regularization process, trivially small correlations were shrunk to zero. This regularization approach may reduce "false positive" edges and result in a network that is more stable and interpretable (36, 38). At the same time, the hyperparameter was set to 0.5 to balance the trade-off between sensitivity and specificity (36, 39). The final network was constructed and visualized [Fruchterman-Reingold algorithm, (40)] by conducting the *R-package qgraph* (41).

To calculate the node expected influence for each node within the final network, the R-package *qgraph* was used (41). Node expected influence is the sum of the edge weights linking to a specific node (42). A node with a higher expected influence is considered statistically more important within the network. The R-package *networktools* were used to compute the node bridge expected influence for each node within the final network (29). Node bridge expected influence is the sum of the edge weights linking a specific node to all nodes within the opposite community. A node with a higher bridge expected influence may be more likely to activate the opposite community (29). There were two communities of nodes in the current network, namely, the IU community (12 items from the IUS-12) and the depression community (9 items from the PHQ-9).

We tested the precision and robustness of the final network using the R package *bootnet* (30). The accuracy of edge weights was examined *via* 2,000 bootstrap samples in a non-parametric bootstrap technique. The correlation stability (CS)-coefficient was used to quantify the stability of node centralities (i.e., node expected to influence and bridge expected influence). Using 2,000 bootstrap samples, a case-dropping bootstrap methodology was used to get the CS coefficients for both metrics. The recommended value for CS-coefficient is above 0.5 and should not be lower than 0.25 (30). We also conducted bootstrapped difference tests to examine the difference between two edge weights or two node centralities.

Results

Descriptive statistics

The common age of the 624 college students (57% female) is 19.38 ± 1.12 years (mean ± SD, varying from 18 to 25 years). Moreover, 246 individuals are sole offspring and 378

individuals are non-sole offspring. The mean scores on the IUS-12 and PHQ-9 are 35.08 ± 7.44 (mean ± SD, range from 15 to 55) and 6.04 ± 4.74 (mean ± SD, range 0–27), respectively. Table 1 listed each variable's abbreviation, mean scores, and standard deviations.

Network structure

The final network was shown in Figure 1. There were several characteristics of this network. First, 127 edges were not zero (about 60%) among 210 possible edges and most of these edges were positive. And we found the six strongest edges in the final network. Among these six strongest edges, four edges were between IU's components IU1 and IU2 (weight = 0.40), IU11 and IU12 (weight = 0.30), IU9 and IU10 (weight = 0.27), IU10 and IU11 (weight = 0.26), and two edges were between D3 and D4 (weight = 0.28), D1 and D7 (weight = 0.24). It is worth noting that these six strongest edges had no one who connects IU's components and depression symptoms. Second, in the 108 possible edges between components of IU and symptoms of depression, 45 edges were not zero that ranged from −0.07 to 0.07. Four strongest edges were between IU2 and D6 (weight = 0.07), IU4 and D8 (weight = 0.07), IU12 and D2 (weight = 0.06), and IU2 and D4 (weight = 0.06). The two weakest edges were between IU7 and D1 (weight = −0.07) and IU7 and D6 (weight = −0.05). Supplementary material 2 showed the values of regularized partial correlation of all edges in the network. Supplementary Figure 1 showed the bootstrapped 95% confidence interval of edge weights and Supplementary Figure 2 showed the bootstrapped difference test for edge weights.

Node expected influence

Figure 2A showed the node expected influence. Two variables with the highest expected influence were D4 "Fatigue" and IU2 "Frustration when facing uncertainty." Thus, from the perspective of statistics, these two variables had the strongest associations with other variables in the present network. The CS-coefficient of node expected influence was 0.67 which indicates that the estimation of node expected influences was adequately stable (Supplementary Figure 3). Supplementary Figure 4 showed the bootstrapped difference test for node expected influences.

Node bridge expected influence

Figure 2B showed the node bridge's expected influence. In the community of depression, two variables with the highest bridge expected influence were D8 "Psychomotor

TABLE 1 Abbreviations, mean scores, and standard deviations for each variable selected in the present network.

Variables	Abbreviation	*M*	SD
Components of intolerance of uncertainty			
IUS-12-1: Unforeseen events upset me greatly	IU1	2.97	1.05
IUS-12-2: It frustrates me not having all the information I need	IU2	2.93	1.06
IUS-12-3: One should always look ahead so as to avoid surprises	IU3	3.52	0.94
IUS-12-4: A small, unforeseen event can spoil everything, even with the best of planning	IU4	2.90	1.01
IUS-12-5: I always want to know what the future has in store for me	IU5	3.23	1.09
IUS-12-6: I can't stand being taken by surprise	IU6	2.81	1.01
IUS-12-7: I should be able to organize everything in advance	IU7	3.35	0.95
IUS-12-8: Uncertainty keeps me from living a full life	IU8	2.67	1.06
IUS-12-9: When it's time to act, uncertainty paralyzes me	IU9	2.80	1.08
IUS-12-10: When I am uncertain I can't function very well	IU10	2.88	1.07
IUS-12-11: The smallest doubt can stop me from acting	IU11	2.58	1.07
IUS-12-12: I must get away from all uncertain situations	IU12	2.44	0.99
Symptoms of depression			
PHQ-1: Anhedonia	D1	0.78	0.69
PHQ-2: Depressed or sad mood	D2	0.73	0.69
PHQ-3: Sleep difficulties	D3	0.81	0.84
PHQ-4: Fatigue	D4	0.89	0.76
PHQ-5: Appetite changes	D5	0.71	0.84
PHQ-6: Feeling of worthlessness	D6	0.66	0.73
PHQ-7: Concentration difficulties	D7	0.81	0.73
PHQ-8: Psychomotor agitation/retardation	D8	0.45	0.66
PHQ-9: Thoughts of death	D9	0.20	0.49

M, mean; SD, standard deviation.

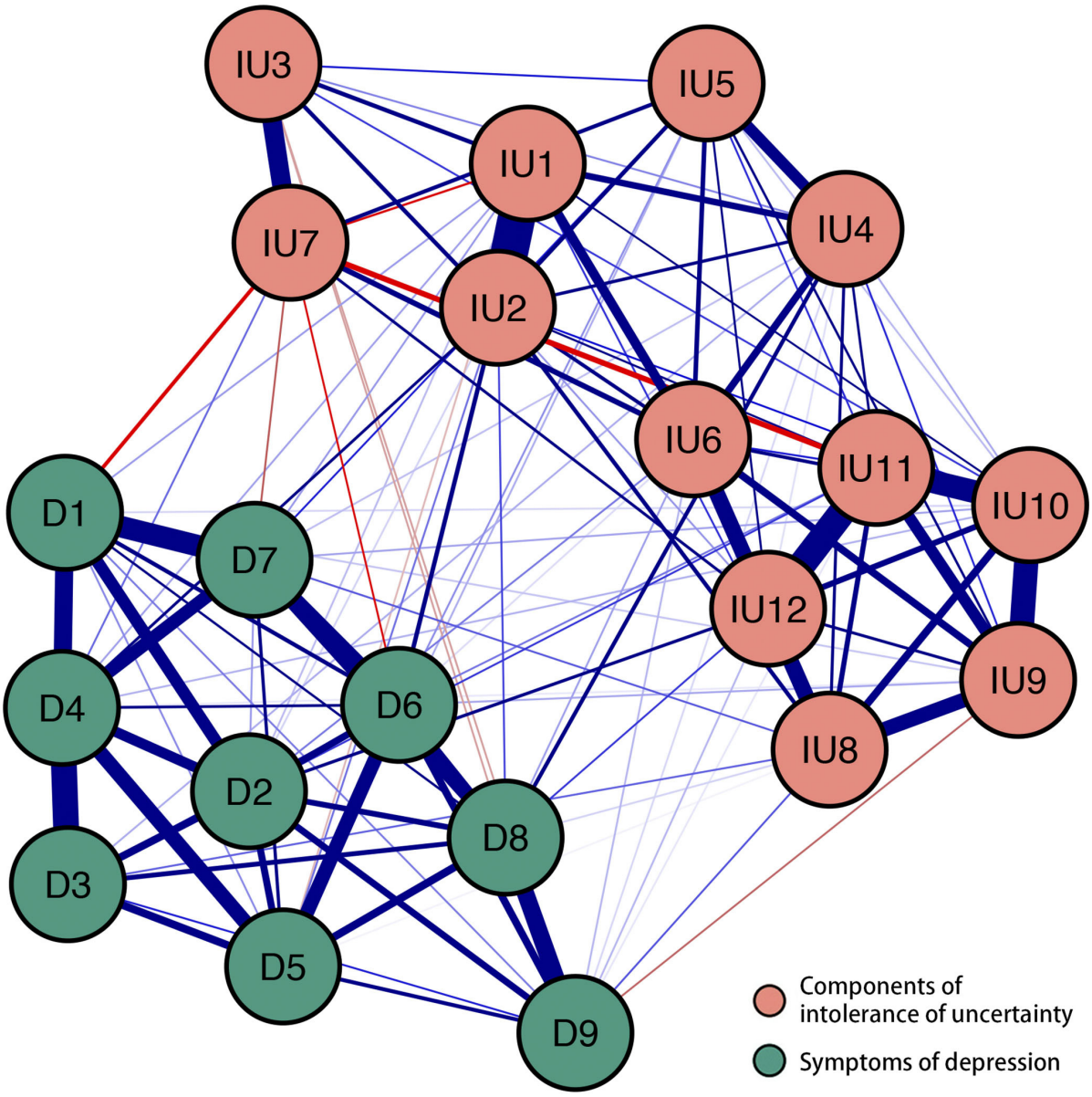

FIGURE 1
The network structure of different components of intolerance of uncertainty and symptoms of depression. Positive correlations were shown by blue borders, whereas negative correlations were represented by red edges. The size of the correlation was reflected in the thickness of the edge. Cut value = 0.05. The text of intolerance of uncertainty and depression can be seen in Table 1.

agitation/retardation" and D2 "Depressed or sad mood." In the community of IU, one variable with the highest bridge expected influence was IU2 "Frustration when facing uncertainty." Thus, from the perspective of statistics, IU2 had the strongest association with depression symptoms. The CS-coefficient of node bridge expected influence was 0.44 (>0.25), indicating that the node bridge expected influence calculation fulfilled the criteria (Supplementary Figure 5). The bootstrapped difference test for node bridge expected influences were shown in Supplementary Figure 6.

Discussion

This was the first study to apply network analysis to examine the differential associations between symptoms of depression and components of IU during the COVID-19 pandemic. We found several pathways between IU and Depression, with the strongest emerging between IU2 "Frustration when facing uncertainty" and D6 "Feelings of worthlessness." Our results also highlighted the important role of IU2, which was identified as both a central node and a bridge node

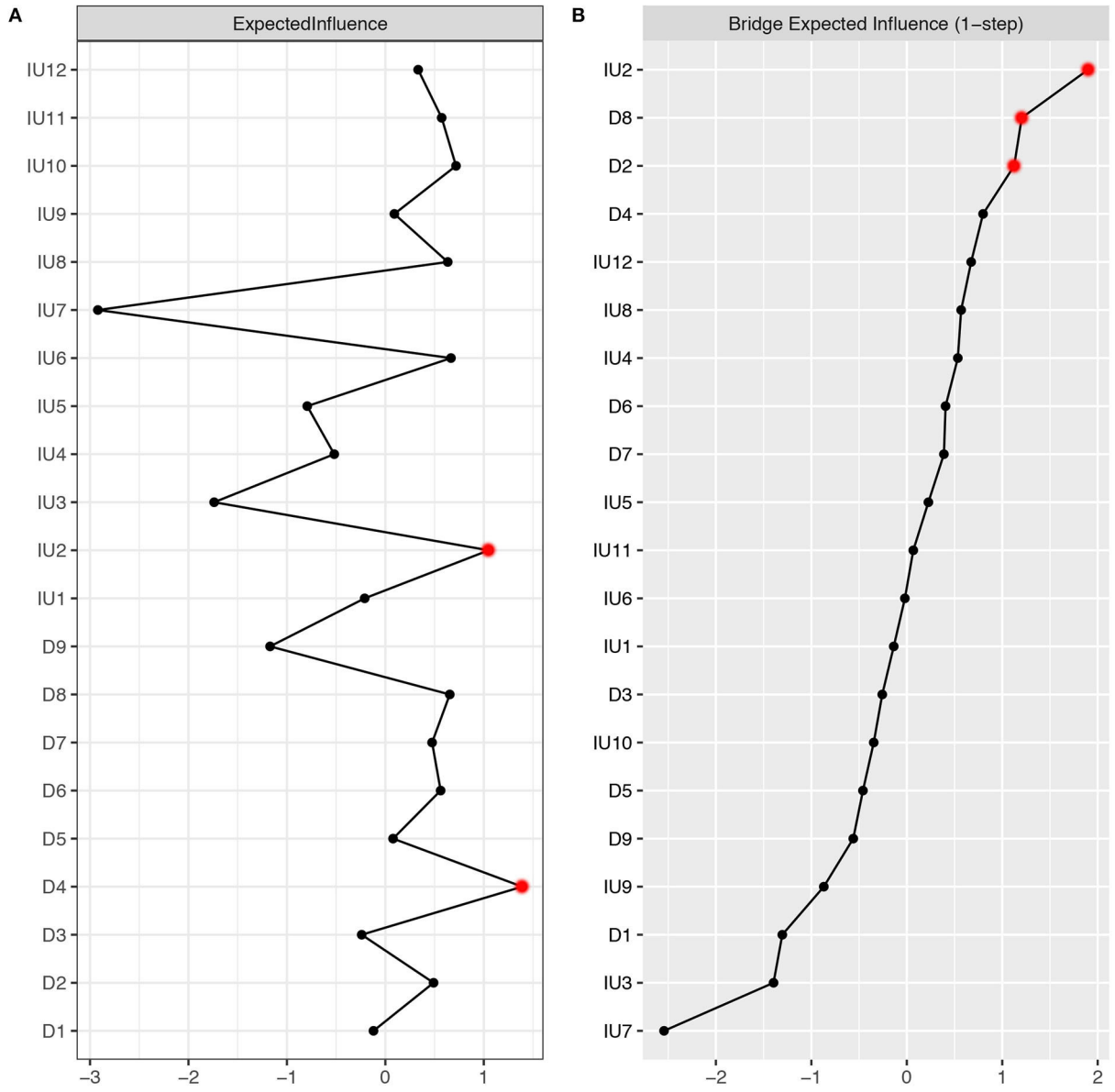

FIGURE 2
(A) Centrality plot depicted the expected influence (z-score) of each variable chosen in the final network. **(B)** Centrality plot depicted the bridge expected influence (z-score) of each variable chosen in the final network. The text of IU and depression can be seen in Table 1.

within the estimated network. Other influential nodes were D4 "Fatigue" (with the highest node expected influence), D8 "Psychomotor agitation/retardation" (with high bridge expected influence), and D2 "Depressed or sad mood" (with high bridge expected influence).

In line with previous studies (24, 25, 43–46), the intra-community connections were generally denser and stronger than the inter-community connections within the estimated network. The strongest intra-community edge emerged between IU1 "Upset when facing unforeseen events" and IU2 "Frustration when facing uncertainty," which was consistently reported in IU-related network analytic studies (24, 25). Within the depression community, we found that D3 "Sleep difficulties" and D4 "Fatigue" were closely related to each other, with "Sleep difficulties" may lead to "Fatigue" and vice versa. This finding is consistent with previous studies exploring the network structure of depression among college students (47, 48), the adult population (17, 49), domestic workers (50), and patients with epilepsy (51). These consistent findings addressed the concerns over the replicability of network analysis (52) and

suggested that some specific symptoms pathway may exist across demographically different groups.

Regarding inter-community pathways, we found IU components may sustain distinct pathways leading to cognitive (e.g., D6 "Feeling of worthlessness"), emotional (e.g., D2 "Depressed or sad mood"), and somatic (e.g., D8 "Psychomotor agitation/retardation" and D4 "Fatigue") symptoms of depression. The strongest pathway was observed between IU2 "Frustration when facing uncertainty" and D6 "Feelings of worthlessness." This pathway may be particularly relevant when considering the cultural context. Specifically, emotional reactions to uncertainty (i.e., feeling frustrated) may be perceived as a lack of self-control or inability to restrain one's emotion, which is considered a major characteristic weakness of an individual and is against related social expectations (53–55). This may, in turn, promote self-hatred cognitions such as a "Feeling of worthlessness." The finding supported the notion that cultural-specific factors should be considered when aiming to understand the maintenance of psychopathology. Specifically, it has been found that the "Feeling of worthlessness" is a uniquely important symptom among individuals from collectivistic cultural backgrounds (e.g., China and India) (56, 57), with unable to fulfill social expectations being proposed as a core mechanism underlying the maintenance of depression (56). Hence, it may be beneficial to replicate our findings among individuals from individualistic cultural backgrounds to ascertain whether cultural differences may impact the putative pathway between IU and depression.

Depression symptom D4 "Fatigue" and IU component IU2 "Frustration when facing uncertainty" showed the highest expected influence, indicating these two variables may be core to the maintenance of the IU-Depression network. The highest expected influence for IU2 is also consistent with our previous network study investigating IU-anxiety and IU-problematic smartphone use networks (24, 25). Depression symptom "Fatigue" is also a core symptom in previous network studies investigating the symptom network of depression-anxiety in college students and Filipino domestic workers (47, 48, 50).

When examining the bridge expected influence, we found that IU2 "Frustration when facing uncertainty," D8 "Psychomotor agitation/retardation," and D2 "Depressed or sad mood" emerged as bridging nodes between the IU and depression communities. As for IU, node bridge expected influence may reveal the unique effect of different components of IU on the various symptoms of depression. IU2 has the highest bridge expected influence. This indicates that IU2 has stronger connections with the depression community than other IU components. Therefore, from the perspective of the network system, targeting IU2 may be more effective at alleviating depression symptoms than targeting other components of IU. It should be noted that this is only a hypothesis, which needs to be tested experimentally and clinically. From the standpoint of concept, people are more likely to fear missing out and tend to get more information about the pandemic due to the uncertainty of the COVID-19 pandemic (58). However, it is almost impossible to obtain all the information about the COVID-9 pandemic. Under this condition, individuals may begin to generate negative emotions, which in turn increase the severity of depression symptoms. It is worth mentioning that IU7 "Organizing everything in advance" has four pathways linking to the depression community and three of them are negative. This leads to its lowest bridge centrality and may represent a protective ability for depression symptoms. In fact, organizing things in advance is a sign of maturity in Chinese culture, which might also symbolize the advantageous response as a substitute for intolerance when dealing with uncertainty (24). In the depression community, symptoms D8 and D2 have the greatest bridge expected influence. This implies that these two depression symptoms might be susceptible to the IU community.

We found that IU2 "Frustration when facing uncertainty" may act as both a central node and a bridge node within the IU-Depression network. This replicated previous findings from networks involving co-occurring anxiety (24) and problematic smartphone use (25). These consistent findings support the notion that IU may act as a transdiagnostic risk factor for various psychological conditions (e.g., emotional disorders, obsessive-compulsive disorder, addiction, and eating disorders) and add incremental value to current knowledge by teasing out the specific component that may underpin the association between IU and psychological conditions. This finding may have implications at the public health level. Specifically, by assessing individual differences in negative emotional reactions (i.e., frustrations) toward uncertainty, mental health providers may be able to identify the high-risk population for developing emotional and addiction-related symptoms. Further, interventions targeting this specific component may concurrently reduce various psychological conditions. This may be particularly relevant to reducing the public mental health burden during and after the pandemic.

Several limitations should be considered when interpreting current findings. First, the utilization of a student sample from a single Chinese university may limit the representativeness of current findings. Second, the current study used a cross-sectional approach. This means that no causal relationship can be established among study variables. Third, the network structure in the current study was examined at a group level and may not be replicable when examined at an individual level.

Conclusion

Notwithstanding the limitations above, the current study has some strengths. To the satisfaction of our knowledge, our study

is the first to apply network analysis to explore the component-to-symptom connections between IU and depression during the COVID-19 pandemic. Findings identify some central and bridge variables (especially IU component IU2 "Frustration when facing uncertainty") in the depression-IU network. These central and bridge variables may also provide some insights for related preventions and therapies to address the COVID-19 pandemic's mental health needs. Based on our results, "Frustration when facing uncertainty" may be a promising target when designing interventions for depression symptoms.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: In order to protect private information, the data cannot be made publicly available. The data may be available from the corresponding author for a reason, and requests to access these datasets should be directed to LR.

Ethics statement

The studies involving human participants were reviewed and approved by the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of the Fourth Military Medical University (Project No.BWS16J012). The questionnaire was completed online in the WeChat application after electronic informed consent was obtained.

Author contributions

TF, LR, HW, and XL developed the study idea and design. TF, LR, and CL wrote the original draft of this manuscript. All authors contributed to revising subsequent versions of the article.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.993814/full#supplementary-material

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Longitudinal development of depression and anxiety during COVID-19 pandemic in Germany: Findings from a population-based probability sample survey

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The stress response to the COVID-19 pandemic might differ between early and later stages. Longitudinal data on the development of population mental health during COVID-19 pandemic is scarce. We have investigated mental health trajectories and predictors for change in a probability sample of the general population in Germany at the beginning and after 6 months of the pandemic. We conducted a longitudinal survey in a population-based probability sample of German adults. The current study analyzed data from a first assessment in May 2020 (T1; $N = 1,412$) and a second in November 2020 (T2; $N = 743$). Mental health was assessed in terms of anxiety and depression using the Patient Health Questionnaire-4 (PHQ-4). Mental health outcomes at T1 were compared with PHQ-4 norm data. Trajectories over time were investigated based on outcome classifications of PHQ-4 scores. Predictors of mental health outcomes and change were identified using multiple regression analysis. In spring 2020, participants showed significantly higher PHQ-4 scores as compared to the norm data, however, overall anxiety and depression remained low also 6 months later. 6.6% of respondents showed a mental health deterioration in autumn 2020, entering subclinical and clinical ranges, outweighing the proportion of people with improved outcomes. Sociodemographic variables associated with mental distress at T1 were mainly not predictive for change at T2. Even under prolonged pandemic-related

stress, mental health remained mainly stable in the general population. Further development of the considerable subgroup experiencing deterioration of depression and anxiety should be monitored, in order to tailor prevention and intervention efforts.

KEYWORDS

anxiety, COVID-19, depression, mental health, pandemic, population

Introduction

From a mental health perspective, the COVID-19 pandemic can be understood as a global stress induction. Large population groups live under recurrent lockdown situations and threat of a potential infection, experiencing a deprivation of resources and rewarding experiences while mostly having limited control and perspective regarding the situation. The course of the pandemic induces different stages and levels of stress which match well with seminal stress models (1, 2): While the first lockdown in spring 2020 might have induced acute stress, the ongoing pandemic might qualify as a chronic stressor. Hence, the pandemic provides us with novel insights into how individuals cope with stress and about who stays healthy and who is specifically vulnerable to adverse outcomes of chronic stress, including the development of mental symptoms and disorders. This knowledge is pivotal to inform government and health care decisions targeting mental health sequelae of the pandemic (3, 4). However, major methodological limitations of the evidence have been criticized, including a wide reliance on convenience samples (5–8) and a lack of longitudinal data (7, 9, 10). Two large representative surveys from the US (11) and UK (12) investigating pre-post-pandemic mental health outcomes found increased distress in the general population early after the COVID-19 outbreak. The few representative longitudinal studies draw a more differential picture: Data comparing multiple assessments during early stages of the pandemic indicate no changes in mental health outcomes (10, 13, 14), or even a decrease in depression and anxiety over the first 20 weeks of lockdown (15). The few representative studies analyzing individual mental health trajectories identify most people as resilient, while 7% to 11% of individuals reported mental health decline (9, 10, 16) vs. 9–12% experiencing improvements (10, 16). This pattern in mental health development over time has also been found in population-based surveys conducted in Germany (17, 18): Based on the same instrument as used in the present study to assess anxiety and depression, an initial increase in anxiety and depression was found in early stages of the pandemic, which was again reduced during the second wave of the pandemic (18), but overall higher scores of anxiety and depression were reported peri-pandemic as compared to pre-pandemic years (17). Consistently, a recent meta-analysis on lockdown effects on population mental health concludes that most individuals stay mentally healthy (8). Importantly, most of these data stem from the initial stage of the pandemic (8–15), a stage of adaption to an acute stressor (1) as well as stepwise withdrawal of lockdown measures (10). However, mental health might be affected differently along the different stages of the pandemic.

We contribute to the evidence on population mental health during the COVID-19 pandemic by presenting longitudinal data from two assessments within a period of 6 months from a probability sample survey in a German metropole region. We used the Patient Health Questionnaire-4 (PHQ-4) (19, 20) as validated self-report instrument to assess symptoms of depression and anxiety in spring 2020 (T1) and in autumn 2020 (T2). The second assessment point was chosen as in autumn 2020, this was the beginning of the second infection wave and also the second lockdown in Germany, and we hypothesized that these circumstances might impact population mental health. At T1, the 7-day incidence of COVID-19 infections was 5.7 / 100.000 inhabitants in Germany and 7.5 in Stuttgart; at T2, the 7-day incidence was 153.1 in Germany and 137.6 in Stuttgart.

We hypothesized that on average, we will find increased levels of anxiety and depression (a) at T1 as compared to representative norm data, and (b) at T2 as compared to T1 due to reapplied lockdown measures. We expected (c) a majority of the sample to be resilient to mental distress and a small group to show trajectories of impaired mental health and (d) that we will be able to identify sociodemographic predictors for increased distress at T1 and the change between T1 and T2. We tested female gender, younger age, lower education background, living alone and living with children as they have been previously identified as predictors for mental distress early in the pandemic (11, 12, 15, 18). Additionally, we looked at Body Mass Index (BMI) as exploratory variable as elevated BMI has been found to be associated with higher levels of anxiety and depression (21) and as BMI is a proxy of eating behavior which, in some individuals, can serve as an emotion regulation strategy under stressful conditions (22).

Methods

The present study is reported according to the STROBE statement (23).

Study design and recruitment

This survey is a subproject of a longitudinal serological investigation of undetected SARS-CoV-2 infection in the general population. Data was derived from a probability sample of the adult general population living in Stuttgart, Germany. Major confinement measures throughout the pandemic, including lockdowns, were in-place on a nationwide level in Germany, hence the situation of the population of Stuttgart is comparable with circumstances in other parts of the country.

Measures

Mental health was assessed in terms of core symptoms of anxiety and depression using the PHQ-4 (19, 20) which is a widely used screening tool comprised of two items assessing anxiety (GAD-2) and two items assessing depressive symptoms (PHQ-2). The PHQ-2 comprises the DSM-IV core criteria for depressive disorders which are assessed for the last 2 weeks (20), while the GAD-2 assesses the two core criteria for generalized anxiety disorder (20), which have been found to be also good screening approaches for panic, social anxiety and post-traumatic stress disorder (24). The PHQ-4 total score, a sum of PHQ-2 and GAD-2 scores, ranges from 0 to 12 with scores $\geq 6 \leq 8$ considered as yellow flag and scores ≥ 9 considered as red flag for the presence of anxiety and depression (20). The PHQ-4 is a very widely used brief screening tool for anxiety and depression with excellent psychometric qualities (20). We additionally assessed sociodemographic variables.

Procedure

Adult members of 4,400 households in Stuttgart were invited *via* postal letters to participate in the study. This initial sample was drawn based on data from the residents' registration office and was representative for the adult population living in Stuttgart. Only one single person was invited per household. The first assessment point took place in the second week of May 2020, which was toward the end of the first pandemic wave in Germany. Study participants were re-invited in the last week of November 2020, which was at the beginning of the second lockdown in Germany. Participants were offered to fill in either a paper or an online version of the survey with identical content. No further exclusion criteria applied.

Ethics statement

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects were approved by the ethics committee of the Medical Faculty Tuebingen and the University Hospital Tuebingen (271/2020BO1). Written informed consent was obtained from all subjects.

Statistical analyses

Primary aim of the study was to investigate mental health trajectories assessed by the PHQ-4 in the general population at the beginning of the pandemic and after 6 months. Predictors for both, baseline and change after 6 months should be identified. For comparison, we used raw data from the PHQ-4 validation study (20). To address responder bias, relevant characteristics at baseline were compared between responders and non-responders using chi-squared test (full df or one df in case of ordinal variables) and *t*-tests (normally distributed data) or Mann-Whitney tests (non-normally distributed data). Normality was assessed by inspection of skewness and kurtosis (both had to be between -1 and $+1$).

PHQ-4 was analyzed quantitatively and according to a classification proposed by Löwe et al. (20) (see above). Like previously applied by other workgroups (10), we had a specific focus on individual trajectories between T1 and T2 and classified the study sample into participants who remained stable within the respective PHQ-4 band (below 6, $\geq 6 \leq 8$ and below 8), those who improved as they were moving to a lower band and those who deteriorated as they were moving to a higher band.

Change of PHQ-4 was assessed by *t*-tests for paired samples (continuous scale), and by sign tests (categorical scale). Associations between quantitative predictors and PHQ-4 at baseline were assessed by linear models (Pearson correlations, ANOVA, including Tukeys B for pairwise comparisons, Curve fit for inspection of quadratic terms, and multiple regression analysis). The same methods were used to assess associations with change of PHQ-4 scores. No imputation was performed and change over time was analyzed only for subjects who participated at T2. This was an exploratory study, thus the chosen level of significance (0.05 two-sided) is not strictly confirmatory and not adjusted for multiple testing. The analyses were carried out using SPSS release 26 (Armonk, NY: IBM Corp). For the Sankey plots, the package R (Vienna, Austria: R Foundation for Statistical Computing) was used.

Results

Sample characteristics

The baseline sample at T1 comprised 1,412 participants (32.1% response rate) with a mean age of 50.7 $\pm$ 18.7 years of which 48.1% were females. 18.3% were living alone, 21.3 %

were living with one or more children (Table 1). 64.5 % were employed, and of those working, 51.6% were predominantly and 27% were completely working from home.

At T2, 743 people (52.8%) participated in the survey. Responders were significantly younger, more often female and reported a lower BMI at baseline. None of the remaining characteristics were different between responders and non-responders (Table 1).

Mental health outcomes at baseline and their predictors

PHQ-4 scores at T1 were significantly higher in our sample as compared to the norm data (see Figure 1).

Higher PHQ-4 scores where observed for younger age ($r = -0.158$, $P < 0.001$), especially for participants between 19 and 24 years (Anova: $F_{(6,1394)} = 8.41$, $\eta^2 = 0.036$, Tukeys B $P < 0.01$,). Females were more affected than males [$t_{(1,399)} = -3.98$, Cohen's d = 0.21, $P < 0.001$]. Figure 1 shows age and gender effects compared to PHQ-4 norm values in the German population. Participants with underweight (BMI < 18.5 kg/m²) and obesity (BMI > 30 kg/m²) were more affected than those with BMI between 18.5 and 30 kg/m² [quadratic term, b = 0.104, $t_{(1,382)} = 3.85$, $P < 0.001$]. People with academic education were less affected than the remaining groups [b = −0.182, $T_{(1,326)} = -4.12$, $P < 0.001$]. There was no effect for the number of children [b = 0.148, $t_{(1,401)} = 1.90$, $P = 0.058$] and an unclear pattern for household size [ANOVA $F_{(4,1,396)} = 3.94$, $\eta^2 = 0.01$, $P = 0.003$, linear trend $P = 0.093$, quadratic $P = 0.048$]. In a multiple regression analysis, all predictors [r^2 adjusted = 0.053, age, b = −0.022, $t_{(1,300)} = -6.17$, $p < 0.001$; gender, b = 0.36, $t_{(1,300)} = 2.96$, $p = 0.003$; BMI linear, b = 0.133, $t_{(1,300)} = 1.69$, $p = 0.092$; BMI quadratic, b = 0.066, $t_{(1,300)} = 2.40$, $P = 0.017$; education, b = −0.133, $t_{(1,300)} = -3.00$, $P = 0.003$] were significant. Results were similar for the subscale PHQ-2 and less pronounced for the subscale GAD-2 (Supplementary material 1).

Longitudinal mental health trajectories

In the quantitative analysis, changes of the PHQ-4 score and the PHQ-2 subscale score were highly significant [cohen's d = 0.16 total, (subscale 0.18), ($t_{(740)} = 4.24$, (4.99), $P < 0.001$ each] whereas the change in the GAD-2 subscale was less pronounced [cohen's d = 0.08, $t_{(740)} = 2.13$, $P = 0.03$] (Table 2). Figure 2 shows that a vast majority of participants (87%) had stable PHQ-4 scores within the good mental health range. Significantly more participants (6.6%, $n = 49$) showed a deterioration of mental health at T2, as compared to those showing a mental health improvement ($n = 49$ vs. $n = 21$, 2.8%, $P = 0.001$, exact binomial test). Most of the deteriorations indicated migrating from good health into the "yellow flag" range and a small proportion moving in the "red flag" range.

Predictors of mental health changes after 6 months

In contrast to the cross-sectional baseline analysis, except for BMI, none of the predictors investigated were significantly associated with the change in PHQ-4 scores (continuous scale) during the observation period. There was a small significant effect (r =-0.087, $P < 0.02$) that participants with a higher BMI showed less deterioration as compared to people with lower BMI.

Discussion

The present longitudinal survey assessed depression and anxiety trajectories over 6 months of the COVID-19 pandemic in a large German population-based probability sample.

We replicated findings showing mental health impairments early in the pandemic (11, 12, 18), with females (18, 25), younger people (18) and people with lower education level being more affected (7). Moreover, we found people on both poles of the BMI spectrum to be more affected, while underweight/obesity might be associated with higher vulnerability toward stress and generally increased mental health burden (21). The BMI-related effects in our sample might partly also mirror current longitudinal trends indicating an increased incidence of eating disorder diagnoses over the first months of the pandemic (26). Regarding potential sex differences in mental health outcomes, it is important to consider several aspects: First of all, longitudinal representative trajectory data on mental health does not report sex differences (10, 15, 16), highlighting again the importance to differentiate between initial and ongoing reaction to the crisis. Secondly, sampling effects could influence data as especially in convenience samples, a significant larger group of participants is female (7). Third, population-based surveys are usually brief and cover the most common mental health outcomes, and while women might just be more likely to endorse symptoms of anxiety and depression, surveys potentially neglect symptoms that are more common experienced in males under stressful conditions (27). Finally, elevated rates of anxiety and depression in females early in the pandemic might partly reflect common gender roles rather than biological sex differences, for instance, women juggling employment and care work under lockdown conditions (27).

Our hypothesis of overall longitudinal deterioration in anxiety and depression 6 months later was supported. Yet, most people remained stable in the range of good mental health, and these individual trajectories support recent evaluations that the mental health of most participants remains stable despite

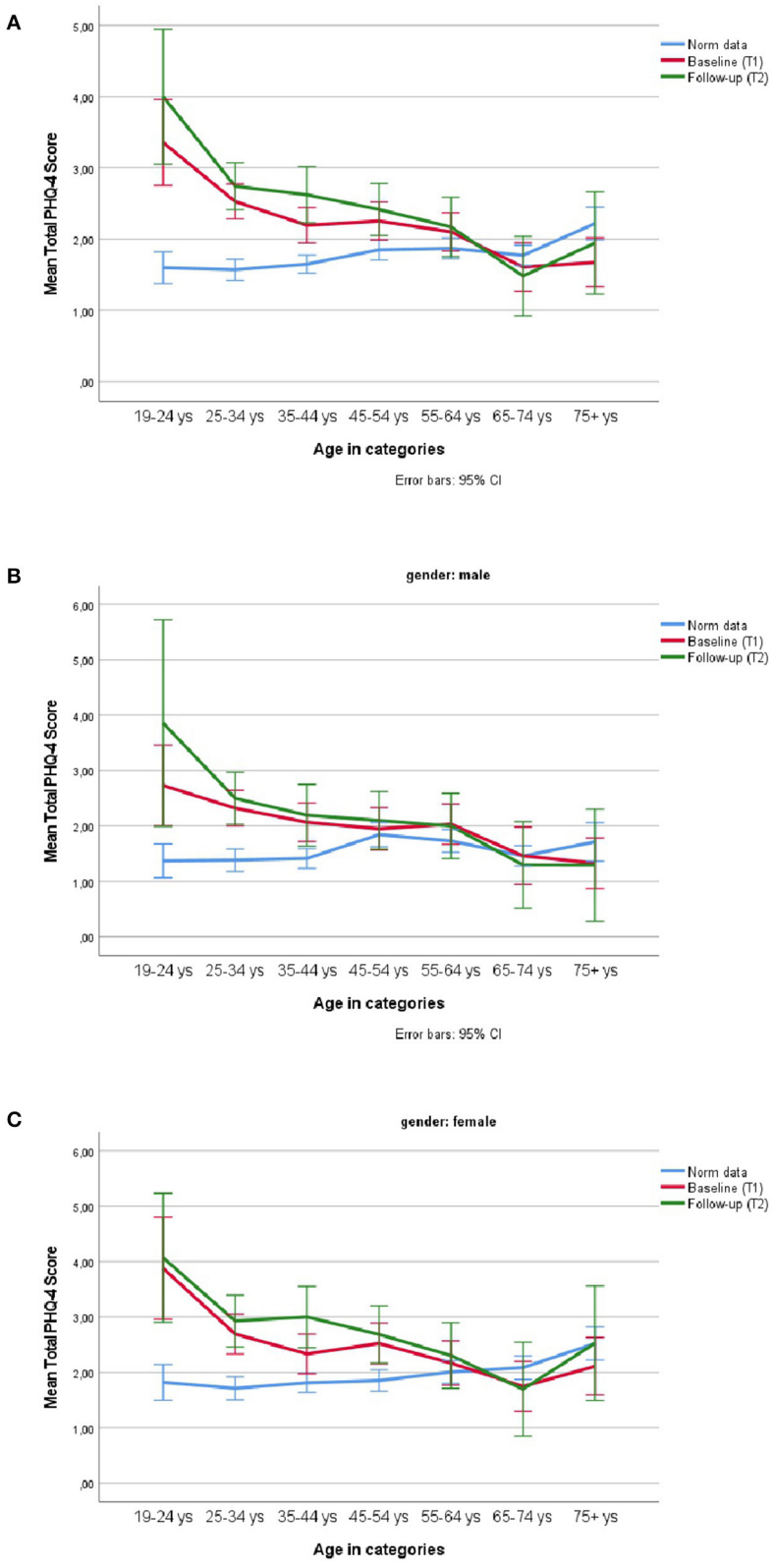

FIGURE 1
PHQ-4 mean scores at T1 and T2 in the survey population as compared to PHQ-4 normative data in different age groups in **(A)** the total sample, **(B)** in males, and **(C)** in females.

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TABLE 1 Sociodemographic variables in survey responders vs. non-responders at follow-up.

Variable	Non-responders in follow-up	*n*	Responders in follow-up	*n*	*P*-value responder bias	Responders in follow-up	*n*	*P*-value follow-up vs. baseline
Age (yrs); M ± SD	50.7 ± 18.7	667	45.3 ± 15.8	741	$<0.001^{MW}$	N.A.		N.A.
Sex; *n* (%)		669		743	0.008^{Chi}	N.A.		N.A.
Male	347 (51.9%)		333 (44.8%)					
Female	322 (48.1%)		410 (55.2%)					
Missing values	0		0					
BMI (kg/m²); M ± SD	25.5 (± 4.6)	659	24.9 (± 4.7)	733	0.001^{MW}	24.8 (± 4.6)	732	0.48^{WT}
Education; *n* (%)		622		711	0.001^{LL}	N.A.		N.A.
None	79 (12.7%)		40 (5.6%)					
Vocational training	220 (35.4%)		232 (32.6%)					
Bachelor degree	63 (10.1%)		91 (12.8%)					
Master degree	120 (19.3%)		177 (24.9%)					
Diploma	140 (22.5%)		171 (24.1%)					
Missing value	47		32					
Persons in household; *n* (%)		667		741	0.36^{LL}	N.A.		N.A.
1	122 (18.3%)		128 (17.3%)					
2	314 (47.1%)		343 (46.3%)					
3	116 (17.4%)		118 (15.9%)					
4	79 (11.8%)		118 (15.9%)					
5 or more	36 (5.4%)		34 (4.6%)					
Missing values	2		2					
Children in household; *n* (%)		668		742	0.14^{LL}	N.A.		N.A.
0	526 (78.7%)		563 (75.9%)					
1	74 (11.1%)		81 (10.9%)					
2	52 (7.8%)		80 (10.8%)					
3 or more	16 (2.4%)		18 (2.4%)					
Missing value	1		1					

pandemic-induced stress (8–10, 16). The trajectory data also matches with our theoretical argument related to assumptions of general stress models (1, 2): Initial increased mental health burden might mirror acute stress in the general population during the first lockdown in spring 2020. Over half a year, the majority of the population shows resilience toward the ongoing pandemic, however there is also a substantial group showing metal health deterioration under this now chronic stress situation. development of mental symptoms and disorders.

In contrast to trajectory data from UK covering earlier time intervals (10, 16), the group in our sample experiencing mental health deterioration was slightly smaller, still, there were clearly more people declining than improving in mental health, while these contrasting groups were nearly equal in the UK surveys (10, 16). Our data covers a comparably longer time interval, re-assessing the sample after reapplication of nationwide lockdown measures in Germany, and this might explain why we found less improvement regarding anxiety and depression. BMI was the only variable predicting mental health change over 6 months, though this effect was small and should be interpreted with caution. However, the evidence on who is vulnerable in the long run of the pandemic is still limited, and also a recent study investigating mental health trajectories concludes that most of the predictors for distress in early pandemic stages were less consistently associated with longitudinal mental health trajectories (10). There is preliminary evidence for pre-existing illness, socioeconomic status and ethnicity to predict long-term mental health deterioration during COVID-19 pandemic (16).

Germany is a high-income country, and, in light of this, it is important to consider that trajectories in population mental health may also be related to the national health and social care systems, as well as specific government responses to the crisis and available resources in the society. Indeed, Germany has taking several measures in order to mitigate the impact

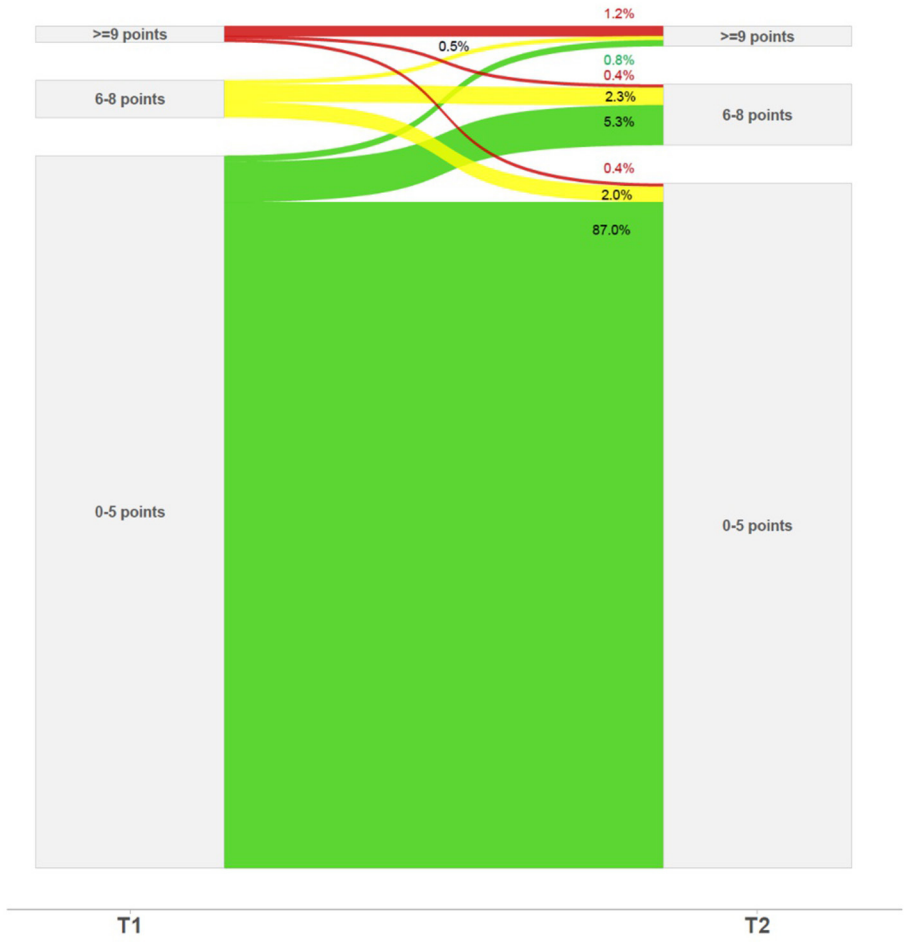

FIGURE 2
PHQ-4 mental health trajectories between T1 and T2.

of the pandemic on people's live circumstance, for instance, financial reimbursement was widely implemented in Germany for individuals unable to work during lockdowns. In contrast, economic uncertainty throughout the pandemic might be more severe and might impact more strongly mental health outcomes in developing countries (28).

Strengths and limitations

In the present study, we report data on longitudinal mental health outcomes during COVID-19 pandemic from a population-based probability sample. As such, it overcomes some of the methodological weaknesses of online survey data (5) which currently forms most of the evidence based on mental health outcomes during the pandemic (7). Our survey participants were invited *via* mail to their postal address, which allows also people to participate who would have been digitally excluded. Our data covers an interval of 6 months, and we rely on a widely used instrument assessing anxiety and depression (20). The PHQ-4 is a brief screening instrument with excellent psychometric qualities (20), allowing for an ecological assessment of mental health outcomes, which is an advantage especially in large surveys. However, at the same time, we did not cover other aspects of mental health, for instance such as insomnia. Further limitations comprise that the study protocol was not pre-registered, we cannot compare to pre-pandemic data; our sample exclusively stems from an urban background, and the survey lacks information about variables which have previously been identified to influence mental health outcomes, such as ethnicity and income (15, 16), sense of coherence (29) or media use (30). The PHQ-4 norm data was published in 2010 which dates back several years from the implementation of the present study. In the course of time, the prevalence of anxious and depressive symptoms might have varied due to factors unrelated to the pandemic. We found a responder bias

TABLE 2 Mental health outcomes in survey responders vs. non-responders at follow-up.

Variable	Non-responders in follow-up	*N*	Responders in follow-up	*n*	*P*-value responder bias	Responders in follow-up	*n*	*P*-value follow-up vs. baseline
PHQ-4 sum score; M ± SD	2.2 ± 2.2	741	2.3 ± 2.2	660	0.94[MW]	2.5 ± 2.4	741	<0.001[WT]
PHQ-4 categorized; *n* (%)		741		660				
Good mental health	690 (92.6%)		608 (92.1%)		0.67[LL]	663 (89.5%)		0.001[ST]
Yellow flag	36 (5.4%)		40 (6.1%)			59 (8.0%)		
Red flag	15 (1.9%)		12 (1.8%)			19 (2.6%)		
PHQ-2 sum score; M ± SD	1.2 (±1.1)	742	1.2 (±1.2)	663	0.95[MW]	1.4 (±1.3)	741	<0.001[WT]
PHQ-2 categorized; *n* (%)					0.46[LL]			<0.001[ST]
Good mental health	671 (90.4%)		592 (89.3%)			634 (85.6%)		
Yellow flag	58 (7.8%)		57 (8.6%)			85 (11.5%)		
Red flag	13 (1.8%)		14 (2.1%)			22 (3.0%)		
GAD-2 sum score; M ± SD	1.0 (±1.2)	741	1.1 (±1.3)	662	0.88[MW]	1.1 (±1.3)	741	0.03[WT]
GAD-2 categorized; *n* (%)					0.98[LL]			0.057[ST]
Good mental health	668 (90.1%)		597 (90.2%)			649 (87.6%)		
Yellow flag	56 (7.6%)		50 (7.6%)			74 (10.0%)		
Red flag	17 (2.3%)		15 (2.3%)			18 (2.4%)		

BMI, Body Mass Index; Chi, Chi square; GAD-2, Subscale assessing depression of the Patient Health Questionnaire-4; LL, linear-by-linear association test; M, mean; MW, Mann–Whitney-U test; PHQ-2, Subscale assessing depression of the Patient Health Questionnaire-4; PHQ-4, Patient Health Questionnaire-4; SD, standard deviation; ST, Sign test; WT, Wilcoxon test.
PHQ categories: Good mental health = sum scores below six for the PHQ-4 and below three for the subscales; Yellow flag = sum scores between six and eight for the PHQ-4 and sum scores of three or four for the subscales; Red flag = sum scores of nine or larger for the PHQ-4 and sum scores of five or larger for the subscales.

between T1 and T2 assessment, however, none of the respective variables was strongly associated with mental health change over time. It should be noted that at T1, the concept of predictors is weaker than in the longitudinal setting at T2.

Perspectives and future studies

Future research efforts are needed for an in-depth investigation of long-term trajectories of mental health throughout the pandemic and also post-pandemic (7). For instance, it will be insightful to analyze the development through winter and spring 2020/21 prolonged lockdown conditions in many countries, but also throughout winter 2022 which was characterized by altered strains and circumstances with a novel virus variant. Taking a longer-term perspective, it will be an important question if elevated mental health burden throughout the pandemic puts individuals at risk to develop clinical mental health conditions, and, on a population-level, if and when overall mental health status recovers to pre-pandemic levels. A further pivotal line of research focuses on predictors of both, mental health deterioration and mental resilience throughout the pandemic on a population level and in vulnerable subgroups (17, 31). Knowledge on such risk and protective factors will inform tailored prevention efforts and intervention strategies for future pandemic circumstances. Beyond, and taking a more global perspective, a stronger differentiation of how population mental health has been affected in countries with different government measures, socio-economic levels and health care systems is necessary in order to better understand which political and administrative interventions might be harmful and helpful.

Conclusions

Our longitudinal population-based study contributes to the literature on mental health outcomes during COVID-19 pandemic by reporting trajectory data beyond questionnaire mean scores. These data show that most individuals remain in a stable and healthy range regarding symptoms of anxiety and depression under prolonged pandemic-related stress. Our study

indicates that vulnerability factors differ over the course of the pandemic: While most of those initially vulnerable to acute stress might quickly adapt (15), other groups vulnerable to long-term effects of stress evolve over time.

Importantly, a considerable subsample did experience a deterioration of depression and anxiety symptoms over 6 months. Research efforts on long-term peri- and post-pandemic trajectories of mental health are needed in order to tailor prevention efforts for future pandemic circumstances (4, 32) and to offer support to vulnerable individuals (4), including adapted dissemination strategies, digital and low-threshold interventions (33).

Data availability statement

Raw data related to the present study will be made available by the corresponding author upon reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee at the Medical Faculty of the University Tübingen and the University Hospital Tübingen. The patients/participants provided their written informed consent to participate in this study.

Author contributions

KEG, GP, JSJ, SE, and FJ designed the study and implemented core study procedures. AD and FS contributed to preparation of the survey and supported survey conduction and data handling. PM is the responsible biostatistician. PM and LMSH conducted the data analysis and prepared the figures. BL provided data for parts of the data analysis. PM, KEG, SZ, and FJ interpreted the data. KEG drafted the manuscript. All authors critically revised it and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.1000722/full#supplementary-material

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Preoperative anxiety during COVID-19 pandemic: A single-center observational study and comparison with a historical cohort

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Background: Preoperative anxiety is a common sensation experienced by patients undergoing surgical interventions. It can influence intraoperative and postoperative management through the activation of the neuroendocrine system, leading to tachycardia, hypertension, pulmonary complications, higher consumption of anesthetic drugs, and increased postoperative pain. Our aim was to investigate the level of preoperative anxiety during the COVID-19 pandemic; we also compared it to the preoperative anxiety of a historical cohort before the outbreak.

Methods: This is a single-center observational study. We enrolled 314 patients during the pandemic from May 2021 to November 2021, and our historical cohort consisted of 122 patients enrolled from July 2015 to May 2016 in the university hospital "Federico II" of Naples. The Amsterdam Preoperative Anxiety and Information Scale (APAIS) and the State-Trait Anxiety Inventory (STAI) were used to evaluate preoperative anxiety. In particular, APAIS measures preoperative anxiety and the need for information, and STAI assesses state and trait anxiety through STAI-Y1 and STAI-Y2, respectively. We analyzed APAIS and STAI scores in our population stratified on the basis of age, gender, marital status, previous surgical experiences, and type of surgery, and we compared them to our historical cohort. Statistical analysis was performed through a *t*-test and ANOVA for parametric data, and the Mann–Whitney and Kruskal–Wallis tests for non-parametric data. Linear regression was used to investigate the correlation between demographic data and the scores of STAI and APAIS in both groups.

Results: Our results showed that state and preoperative anxiety remained stable, whereas trait anxiety increased in all the subgroups analyzed.

Discussion: Even if state anxiety is considered a variable characteristic of the emotional sphere and trait anxiety a stable element, our findings suggested that COVID-19 deeply influenced trait anxiety, thus altering the patients' psychological foundations.

KEYWORDS

anxiety, preoperative period, test anxiety scale, psychology, COVID-19 pandemic

Introduction

Anxiety is a common unpleasant sensation experienced by many patients undergoing surgical procedures all over the world (e.g., USA 20–50%, Europe 27–70%, India 31–46%, and Africa 47–70%). It is defined as a stress response to an unfocused threat, whereas fear is defined as the reaction to a specific danger (1–12). Anxiety can cause a state of exaggerated alertness, often in association with physical and psychological symptoms, such as restlessness, fatigue, muscular tension, sweating, tachycardia, increased blood pressure, intrusive thoughts, and difficulty maintaining concentration (8, 13, 14). Physical symptoms are triggered by the activation of the autonomic nervous system, which leads to the neuroendocrine response through an augmented release of many hormones, such as catecholamines, cortisol, and prolactin, thus increasing the risk of both intraoperative and postoperative complications, such as hemodynamic instability, pulmonary complications, and mental disorders, and higher consumption of anesthetic drugs (15–17). Some studies showed that gynecological elective surgical patients with a high anxiety trait need an increased dose of propofol for the induction and maintenance of anesthesia, while anxious patients undergoing cholecystectomy have a higher risk of intraoperative hemodynamic events (15, 16). Moreover, as previously reported, the correlation between preoperative anxiety and the reduction of pain threshold leads to an increased requirement for analgesic drugs (14, 18–22).

Preoperative anxiety can have a multifactorial origin as it can be influenced by gender, age, social status, and previous surgical experiences (23, 24).

Notably, anxiety can lead to an impairment of the immune system and, consequently, to a higher risk of infections (25).

Our study aimed to determine the level of preoperative anxiety during the COVID-19 pandemic; in addition, we compared it to the preoperative anxiety of a population screened in a previous study conducted in our center to investigate if there is any difference between pre-pandemic and pandemic times (26).

Materials and methods

The present study was approved by the local ethic committee "Comitato Etico Università Federico II" (protocol number: 155/20). After explaining the purpose of our research and obtaining written informed consent, we enrolled 314 patients undergoing elective surgery between May 2021 and November 2021 at University Hospital "Federico II" of Naples; they were asked to fill out the questionnaires during the pre-surgical anesthesia assessment. The historical cohort was obtained from the database of a previous study that we conducted before the pandemic (from July 2015 to May 2016) on 122 patients to validate the Italian version of APAIS in the same hospital (27).

The inclusion criteria were as follows: patients in the age bracket of 18–75 years, with adequate language skills, and appropriate comprehension of the questionnaires.

The exclusion criteria were as follows: patients undergoing emergency surgery or obstetric procedures, patients enrolled in our previous study, patients with psychiatric diseases, and patients using psychotropic drugs.

We recorded the following data: anthropometric measures, marital status, educational level, family status, medical and clinical history, and previous surgery. We used two tests to investigate preoperative anxiety, the STAI questionnaire, which is divided into two sections each of them consisting of 20 questions (Y1 and Y2), and the APAIS, a 6-item questionnaire. STAI Y1 was used to measure state anxiety, whereas STAI-Y2 assessed trait anxiety of the patients. State anxiety is defined as a transitory emotional response, whereas trait anxiety is a stable psychological characteristic of the individual, describing the probability to feel anxious in a distressing situation (28). Furthermore, we used APAIS to evaluate not only the anxiety related to anesthesia and the surgery but also the need for information about them. The higher the scores of STAI and APAIS, the higher the level of anxiety of the patient.

Statistical analysis

We first performed a Shapiro–Wilk test to assess the normal distribution of the data. Parametric data were presented

TABLE 1 Demographic characteristics of the study population.

	Pre-pandemic		During-pandemic		
	N (%)	Mean (SD)	*N* (%)	Mean (SD)	*P*-value
All	122 (100%)		314 (100%)		
Age (years)	122 (100%)	50.1 (14.26)	314 (100%)	48.05 (16.62)	0.072
18–29	14 (11%)	24.42 (3.39)	44 (14%)	23.79 (3.36)	0.54
30–39	11 (9%)	34.38 (3.73)	62 (20%)	34.64 (3.03)	0.78
40–49	29 (24%)	43.86 (2.91)	73 (23%)	44.87 (2.3)	0.06
50–59	26 (21%)	54.73 (2.77)	51 (16%)	55.19 (2.72)	0.48
>60	42 (32%)	65.45 (4.95)	84 (17%)	67.28 (4.96)	0.056
Gender					<0.001
Male	70 (57%)		93 (30%)		0.07
Female	52 (43%)		221 (70%)		<0.001
Height (cm)	168.05 (8.337)		164.82 (37.34)		0.261
BMI (kg/cm^2)	168.05 (8.337)		164.82 (37.34)		0.190
Marital status					0.001
Married	98 (80%)		202 (64%)		<0.001
Not married	24 (20%)		112 (36%)		<0.001
Race					0.925
Caucasic	122 (100%)		312 (99%)		
Asian	0 (0%)		2 (1%)		
Comorbidity					<0.001
Yes	38 (31%)		236 (75%)		<0.001
No	84 (69%)		78 (25%)		0.63
Previous surgery					<0.001
Yes	111 (90%)		79 (25%)		0.02
No	11 (10%)		235 (75%)		<0.001
ASA					<0.001
I	20 (16%)		39 (12%)		0.001
II	73 (60%)		233 (74%)		<0.001
III	28 (23%)		38 (12%)		0.21
IV	1 (1%)		0 (0%)		0.31
Type of surgery					<0.001
Minor	20 (17%)		44 (14%)		1
Intermediate	59 (48%)		53 (18%)		<0.001
Major	43 (35%)		217 (68%)		<0.001

as mean and standard deviation, non-parametric data as median and interquartile range, and categorical variables as frequencies. Parametric data were analyzed through Student's *t*-test and the analysis of variance (ANOVA), non-parametric data were analyzed through the Mann–Whitney and Kruskal–Wallis tests, and Pearson's chi-square test was used to compare frequencies. *Post hoc* analyses were performed with Tukey's test for parametric data and Dunn's test for non-parametric data. We conducted a multivariate analysis through a linear model to correlate STAI-Y1, STAI-Y2, and APAIS scores to the demographic data such as age, gender, marital status, previous surgery, and type of surgery. Differences were considered statistically significant if $p < 0.05$. All tests were performed using R Studio (28).

Results

We collected data from 122 patients before the pandemic and 314 patients during the pandemic. Socio-demographic characteristics are reported in Table 1. The two groups differed in gender composition, marital status, comorbidity, previous surgery, American Society of Anesthesiologists (ASA) status, and type of surgery. Table 2 reports the analysis of STAI-Y1; there was no difference in the scores reported by the two groups

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TABLE 2 STAY-Y1 score for pre-pandemic and during-pandemic groups.

	Pre-pandemic		During pandemic		*P*-value
	N **(%)**	**Median (Q1–Q3)**	***N*** **(%)**	**Median (Q1–Q3)**	
All	122 (100%)	43 (35–51)	314 (100%)	45 (42–49)	0.05
Age (years)					
18–29	14 (11%)	45.5 (32.5–54.25)	44 (14%)	46 (42–48)	0.799
30–39	11 (9%)	36 (32–49)	62 (20%)	45 (42–49.5)	0.021
40–49	29 (24%)	42 (35.5–42)	73 (23%)	45.5 (42–49)	0.48
50–59	26 (21%)	45.5 (33.75–59.75)	51 (16%)	45 (40–49)	0.944
>60	42 (32%)	43.5 (37–50.75)	84 (17%)	45 (42.25–48)	0.189
p-value		0.809		0.954	
Gender					
Male	70 (57%)	32.5 (32–44)	93 (30%)	46 (43–49)	<0.001
Female	52 (43%)	47 (36.5–56)	221 (70%)	45 (41–49)	0.57
p-value		<0.001		0.151	
Marital status					
Married	98 (80%)	43.5 (36–51)	202 (64%)	45 (42–49)	0.058
Not married	24 (20%)	39 (33–51.25)	112 (36%)	44 (41–48)	0.262
p-value		0.459		0.033	
Previous surgery					
Yes	111 (90%)	43 (36–51)	79 (25%)	45 (41–48)	0.425
No	11 (10%)	38 (32–52)	235 (75%)	46 (42–49)	0.145
p-value		0.426		0.374	
Type of surgery					
Minor	20 (17%)	47.5 (35.5–47.5)	44 (14%)	44 (41.25–48.75)	0.728
Intermediate	59 (48%)	43 (37–52)	53 (18%)	46 (41–49)	0.413
Major	43 (35%)	39 (33–50)	217 (68%)	45 (42–49)	0.09
p-value		0.33		0.9	

except for the subgroups of patients aged 30–39 years old and men, which showed an increased level of state anxiety during the pandemic.

Table 3 shows that STAI-Y2 scores were significantly higher in the during-pandemic subgroups than in pre-pandemic ones, except for the subgroups aged 50–59 years old and subjects undergoing minor surgery.

Table 4 shows the overall APAIS score. No significant differences were detected between pre- and during-pandemic groups, except for men and patients undergoing minor surgery, which showed a lower score during the pandemic.

Supplementary Table 1 reports the score obtained from the sum of APAIS questions about the anxiety correlated to anesthesia and surgery; men experienced a lower level of anxiety during the pandemic compared to the pre-pandemic group. In both groups, it is confirmed that women are more anxious than men about anesthesia and surgery.

Supplementary Table 2 shows the score obtained from the sum of APAIS questions about the need for information about anesthesia and surgery. No significant differences were recorded between pre- and during-pandemic groups.

Multivariate analysis showed that during the pandemic, STAI-Y1 is inversely correlated to age between 30 and 39 [standardized beta coefficient −2.71, 95% confidence interval (CI): (−5.34; −0.08), *p*-value: 0.043], while no correlation was found between STAI-Y1 score and the other demographic data analyzed both during and before the pandemic (Supplementary Table 3). STAI-Y2 score inversely correlated only to the male gender before the pandemic (standardized beta coefficient: −3.44; 95% CI: −6.60; −0.29, *p*-value: 0.033; Supplementary Table 4). APAIS score inversely correlated to the male gender both before the pandemic (standardized beta coefficient: −2.54, 95% CI: −4.70; −0.37, *p*-value: 0.022) and during the pandemic (standardized beta coefficient: −3.94, 95% CI: −5.62; −2.25, *p*-value: < 0.001) and inversely correlated to age more than 60 during the pandemic (standardized beta coefficient: 3.16, 95% CI: −5.69; −0.62, *p*-value: 0.015; Supplementary Table 5).

Discussion

Our study aimed to investigate the difference in preoperative anxiety before and during the pandemic. We found that

TABLE 3 STAY-Y2 score for pre-pandemic and during-pandemic groups.

	Pre-pandemic		During pandemic		*P*-value
	***N* (%)**	**Median (Q1–Q3)**	***N* (%)**	**Median (Q1–Q3)**	
All	122 (100%)	37.5 (30.75–44)	314 (100%)	46 (42–49)	<0.001
Age (years)					
18–29	14 (11%)	35.5 (29.5–42.75)	44 (14%)	47 (43–49)	<0.001
30–39	11 (9%)	33 (30–42)	62 (20%)	45.5 (41–48.25)	<0.001
40–49	29 (24%)	36 (31.5–42)	73 (23%)	44 (41–48)	<0.001
50–59	26 (21%)	40.5 (34.25–49.25)	51 (16%)	45 (41–50)	0.031
>60	42 (32%)	38 (29.25–42.75)	84 (17%)	46 (43–49.75)	<0.001
p-value		0.482		0.135	
Gender					
Male	70 (57%)	36 (29–42)	93 (30%)	46 (42–48.5)	<0.001
Female	52 (43%)	40 (33–45)	221 (70%)	46 (41–49)	<0.001
p-value		0.08		0.679	
Marital status					
Married	98 (80%)	38 (32–44)	202 (64%)	45 (42–49)	<0.001
Not married	24 (20%)	35.5 (30–42)	112 (36%)	46 (41–49)	<0.001
p-value		0.308		0.78	
Previous surgery					
Yes	111 (90%)	38 (32–44)	79 (25%)	44 (41–48)	<0.001
No	11 (10%)	32 (29–35)	235 (75%)	46 (43–49)	<0.001
p-value		0.083		0.081	
Type of surgery					
Minor	20 (17%)	42.5 (36.75–42.5)	44 (14%)	46.5 (41–48)	0.094
Intermediate	59 (48%)	38 (30-44)*	57 (18%)	45 (42.5–48.5)	<0.001
Major	43 (35%)	34 (29–41)†	217 (68%)	46 (41.5–49)	<0.001
p-value		0.005		0.9	

*There is a statistically significant difference between intermediate and minor surgery ($p = 0.046$).
†There's a statistically significant difference between major and minor surgery ($p < 0.001$).

according to STAI-Y1, there were no significant changes in state anxiety; this result was confirmed by APAIS, which did not show any modification during the pandemic for both the anxiety and the need for information subscales. Notably, all the subgroups analyzed showed increased trait anxiety during the pandemic, as recorded by STAI-Y2.

A possible explanation of this result might be the measures adopted to face the spread of the infection in the hospital; in fact, there was close monitoring of patients before admission to the hospital, checking for the virus infection through nasopharyngeal swabs. Apparently, this initial screening probably made the patient feel safe from the contagion.

Previous studies confirmed our result that age does not significantly affect preoperative anxiety, even during the COVID-19 pandemic; only older patients showed a significantly higher level of perioperative anxiety measured by APAIS during the pandemic, maybe because they felt to be a more fragile category of patients based on information conveyed by mass media (23). According to STAI-Y1, only young adults seemed to experience a higher level of anxiety during the pandemic compared to the pre-pandemic period, probably due to their greater and easier access to the internet and social media, which may have increased the exposure to misinformation; furthermore, men showed an increased level of state anxiety during the pandemic (29). This finding is in contrast with the APAIS score, which showed that during the pandemic preoperative anxiety about anesthesia and surgery in men was lower than in the pre-pandemic period; it is important to underline that APAIS questions are specifically focused on anesthesia and surgery, while STAI-Y1 questions are more generic and the patient could forget that the questionnaire refers to the procedures they will undergo (30). In addition, our data confirmed that both during and before the pandemic, the level of preoperative anxiety was lower in men than in women (23).

In accordance with other studies, previous surgical experiences, type of surgery, and marital status did not influence preoperative anxiety both during and before the pandemic (23, 31, 32).

TABLE 4 The Amsterdam Preoperative Anxiety and Information Scale (APAIS) score for pre-pandemic and during-pandemic groups.

	Pre-pandemic		During pandemic		*P*-value
	***N* (%)**	**Median (Q1–Q3)**	***N* (%)**	**Median (Q1–Q3)**	
All	122 (100%)	15 (10–21)	318 (100%)	15 (11–21)	0.834
Age (years)					
18–29	14 (11%)	17.5 (11.75–20.5)	44 (14%)	15 (7.25–20)	0.16
30–39	11 (9%)	14 (11–21)	62 (20%)	16.5 (12–23.25)	0.521
40–49	29 (24%)	16 (12.5–18)	73 (23%)	15 (10–20.75)	0.941
50–59	26 (21%)	17 (10.75–22)	51 (16%)	14 (10–20)	0.493
>60	42 (32%)	14.5 (10–21.75)	84 (17%)	16 (12–20.75)	0.748
p-value		0.881		0.339	
Gender					
Male	70 (57%)	14 (10–18)	93 (30%)	12 (6–12)	0.011
Female	52 (43%)	17 (12.5–22)	221 (70%)	17 (12–22)	0.893
p-value		0.029		<0.001	
Marital status					
Married	98 (80%)	15 (11–21)	202 (64%)	15 (10–21)	0.649
Not married	24 (20%)	14.5 (10.25–19.5)	112 (36%)	15 (10–21)	0.786
p-value		0.633		0.768	
Previous surgery					
Yes	111 (90%)	15 (11–21)	79 (25%)	15 (9–21)	0.911
No	11 (10%)	15 (11–20)	235 (75%)	15 (10–21)	0.854
p-value		0.778		0.988	
Type of surgery					
Minor	20 (17%)	17 (10–22)	44 (14%)	12 (6–16)	0.02
Intermediate	59 (48%)	16 (11–21)	57 (18%)	15 (10–20.5)*	0.51
Major	43 (35%)	14 (11–20)	217 (68%)	17 (12–21)†	0.168
p-value		0.695		<0.001	

*There is a statistically significant difference between intermediate and minor surgery ($p = 0.046$).
†There is a statistically significant difference between major and minor surgery ($p < 0.001$).

Notably, while overall anxiety did not seem to be substantially affected by the pandemic, trait anxiety augmented in all the subgroups. These findings agree with previous studies investigating trait anxiety in different populations during the pandemic. Trait anxiety is a relatively stable characteristic of a patient's psychology, but it can be modified by many factors such as psychological therapies; we found that the psychological burden of the pandemic was so powerful to be able to alter the hardcore of people's emotional sphere (30, 33). The COVID-19 pandemic did impact the socio-economic, relational, and working aspects as well, and all these factors can profoundly influence the patient's mood (34–38).

Our study has some limitations. First, pre-pandemic and during-pandemic groups are not homogenous in gender, comorbidity, previous surgery, and type of surgery. Notably, all the above-mentioned differences recorded in our groups were supposed to lead to a higher level of state anxiety during the pandemic, but we found that state anxiety was not significantly different between before and during the pandemic. Second, we investigated preoperative anxiety in our hospital; consequently, our findings must be cautiously interpreted and cannot be generalized.

In conclusion, preoperative anxiety is a fundamental issue for many patients undergoing elective surgery, and it could influence perioperative management. The COVID-19 pandemic had an important impact on the psychology of people. Our work highlighted that even if the anxiety related to surgery and anesthesia was not significantly modified during the pandemic, the COVID-19 outbreak has been able to deeply alter the emotional sphere of the patient, revealing that trait anxiety is not an unchangeable characteristic of the subject, but it can be modeled by important socio-economic changes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by "Comitato Etico Università Federico II".

The patients/participants provided their written informed consent to participate in this study.

Author contributions

PB conceived the study and supervised the work. AM wrote the manuscript. MV conducted statistical analyses. CI helped to supervise the project. SN collected and organized the data. AS analyzed the data and drafted the manuscript. GS critically revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.1062381/full#supplementary-material

SUPPLEMENTARY TABLE 1
APAIS anxiety score for pre-pandemic and during-pandemic groups.

SUPPLEMENTARY TABLE 2
APAIS need for information score for pre-pandemic and during-pandemic groups.

SUPPLEMENTARY TABLE 3
Standardized beta coefficients of multivariate analysis analyzing the relationship between during and pre-pandemic STAI-Y1 score and demographic data.

SUPPLEMENTARY TABLE 4
Standardized beta coefficients of multivariate analysis analyzing the relationship between during and pre-pandemic STAI-Y2 score and demographic data.

SUPPLEMENTARY TABLE 5
Standardized beta coefficients of multivariate analysis analyzing the relationship between during and pre-pandemic APAIS score and demographic data.

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Work-related stress of companies' directors during the first lockdown due to the COVID-19

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Background: The COVID-19 pandemic and the first lockdown were particularly stressful with a major economic impact, but the impact on stress of company directors was not known. Therefore, this study aimed to assess that impact and the characteristics of companies the most at risk.

Method: A online questionnaire was sent to 13,114 company. It assessed stress at work, number of employees, sector of activity, business activity rate and geographical location. It studied the mean stress levels, the percentage of stress > 8/10 and carried out an analysis of the characteristics of the most at-risk companies.

Results: A total of 807 company directors responded. Their stress levels increased by 25.9% during lockdown and 28.7% of them had a stress > 8/10. Sectors which had the biggest increase in stress levels during lockdown were retail trade, wholesale trade, and nursing homes. Sectors the most at risk of stress >8/10 during lockdown tended to be nursing homes, pharmacies, and IT activities. Biggest companies had the highest increase in stress levels.

Conclusion: The first lockdown of the COVID-19 pandemic had a major impact on the stress of company directors. Directors of large companies were the most exposed to stress as well as medical and IT activities.

KEYWORDS

stress at work, company directors, lockdown, COVID-19 pandemic, occupational health

1. Introduction

Stress at work is a major issue, causing both physical (1–3) and mental (4, 5) pathologies, but also with a strong economic impact. Most studies on stress at work focus on stress of employees (6), but very few on stress of company directors (7). In this context, the coronavirus disease (COVID-19) pandemic (8), with a global lockdown of half of the world's population created a particular stressful climate that also likely impacted company directors. While very few studies assessed mental health of company directors in relation to the COVID-19 pandemic, they focused on anxiety (9), depression, and burnout (10, 11), but only one assessed stress at work (12). Moreover, none of the aforementioned study retrieved the evolution of stress of company directors before, during, and after the first global lockdown. The COVID-19 outbreak severely disrupted the global economy and impacted gross domestic products (13). All economic sectors have been affected (14). Some experienced an overload of activities such as health or informatics (IT) sectors, while others had to stop such as non-essential businesses. Despite aforementioned studies searched for risk factors of mental health disorders, none evaluated the impact of economic sectors on stress levels of company directors during the COVID-19 pandemic. In all cases and whatever the number of their employees, company directors have had to adapt to new and changing operating rules and to a major impact on their economy (15). Lastly, even if some of previous studies computed regression analyses, they did not quantity the risk of stress depending on characteristics of companies. We hypothesize that a follow-up (before, during and after lockdown) will detect the most at-risk directors to begin rapid action and to build efficient preventive strategy (16).

Therefore, the main aim of this study was to assess the stress of company directors, across the first stages of the pandemic (before, during, and after the first global lockdown). Secondary aims were to study the characteristics of companies the most at-risk of stress–particularly the impact of economic sectors, and to quantify the risk of stress of company directors.

2. Materials and methods

2.1. Study design

The main occupational health department of Auvergne, France, followed 14,148 companies at the time of the first wave of the COVID-19 pandemic. An online questionnaire was sent at the beginning of July 2020 to all the company directors followed by the occupational health department of Clermont-Ferrand without any selection or randomization. We defined company director as those who are at the top of the firm. The questionnaire was sent by email, and anonymized. Those who did not provide an email address were excluded. The study was approved by the ethics committee (CPP Sud-Est VI Clermont-Ferrand) and registered on ClinicalTrials.gov number NCT04308187).

2.2. Outcomes

The main objective was to assess the stress of company directors using three visual analog scales over three time periods. The three VAS were the same in size and methodology. The first one was before French lockdown (i.e., before March 17, 2020), during French lockdown (i.e., between March 17 and May 10) and after French lockdown (i.e., after May 11). Visual analog scale is a validated tool used by occupational physicians to assess stress at work (17, 18). Visual analog scale (VAS) has been validated for the assessment of stress in clinical practice (8) and is currently used by occupational physicians to quickly identify the most stressed people requiring urgent action (9). The use is simple to implement, easy to understand, and quick to execute (19). Visual analog scales are horizontal non calibrated line ranging from minimal (0) to maximal (10) stress. A level of stress higher than 8/10 is a cut-off for stress levels requiring urgent action (20). The secondary outcomes were the sector of activity (secondary or tertiary, main sectors and other sectors studied), the working status during the lockdown [business activity ranging from decreased (0) to increased (10)], the size of the company (number of workers) and the geographical location (metropolis and countryside). Companies were classified according to the variation rate in their activity between before and during lockdown. Those with a greater than average reduction in activity were categorized as "reduced work" and the others as "continued work."

2.3. Statistical analysis

Statistical analysis was performed using Stata software (version 16; StataCorp, College Station, Texas, USA). All tests were two-sided, with a Type I error set at 0.05. Categorical variables were expressed as number of subjects and associated percentages, and quantitative variables as mean ± standard deviation (especially stress level). The evolution of stress over time was evaluated using linear mixed models (for VAS of stress) or generalized linear mixed models with logit link function (for stress level >8/10). Furthermore, the stress variation between before and during lockdown was calculated (VAS during minus VAS before) and the factors associated with this variation were studied using Hedges'g effect sizes (ES). They were presented with 95% confidence intervals (CI) and interpreted according to Cohen's recommendations: 0.2 = small effect, 0.5 = medium effect and 0.8 = large effect. Finally, factors associated with stress >8/10 during lockdown were studied using logistic regressions. The results were expressed as odds ratio (OR) and 95% CI.

3. Results

3.1. Population

The questionnaire was sent to the 13,114 company directors who had provided an email address (Figure 1). A total of 860 responded. Fifty-three were excluded due to incomplete data and analysis were performed on 807 (6.2%). The main sector of activity was the tertiary sector ($n = 576$, 71.4%), essentially market ($n = 456$, 56.5%). The most represented activities were construction trade ($n = 103$, 12.9%), retail trade ($n = 85$, 10.5%) and wholesale trade ($n = 55$, 6.8%). The majority of companies had one to nine employees ($n = 516$, 64.0%), or 10 to 249 employees ($n = 265$, 32.8%); with mainly companies <50 employees ($n = 194/265$, 73.2%). Companies with no employees ($n = 10$, 1.2%) and ≥ 250 ($n = 16$, 2.0%) were poorly represented. The respondent companies were mainly located in the countryside ($n = 492$, 61.0%). The business activity rate decreased by 51.7% with lockdown (5.8 ± 2.0 vs. 2.8 ± 2.8, $p < 0.001$)−49.4% ($n = 398$) were classified as continued working and 50.6% ($n = 407$) as stopped working (Figure 2). The business activity rate remained decreased during and improved after the lockdown while remaining 16.0% lower than initial (5.8 ± 2.0 vs. 4.8 ± 2.6, $p < 0.001$) (Appendix 1).

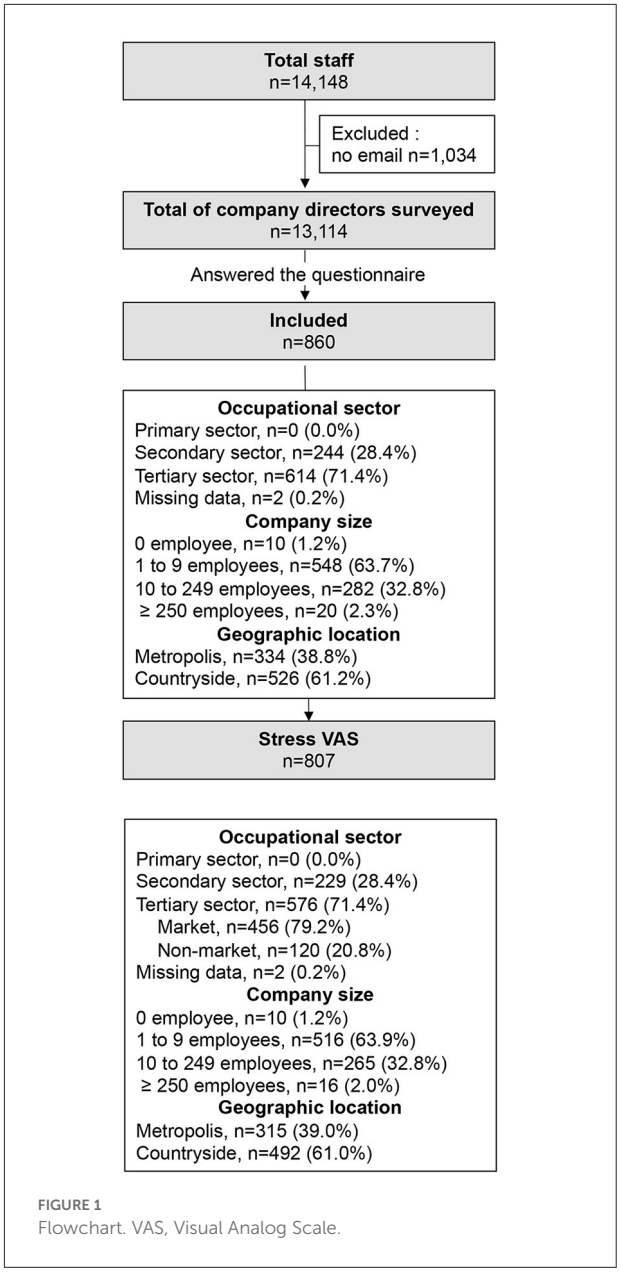

FIGURE 1
Flowchart. VAS, Visual Analog Scale.

3.2. Stress of company directors

The level of stress at work increased by 25.9% during the first lockdown (6.8 ± 2.6 vs. 5.4 ± 2.3, $p < 0.001$) and remained 20.4% higher after (6.5 ± 2.4 vs. 5.4 ± 2.3, $p < 0.001$). The percentage of company directors with a level of stress > 8/10, intervention threshold, was 5.9% ($n = 48$) before lockdown. It increased to 28.7% ($n = 231$, $p < 0.001$) during, remaining at 20.7% after ($n = 167$, $p < 0.001$) (Figures 2, 3).

3.3. Influencing factors of stress of company directors

3.3.1. Longitudinal analyses

Stress of company directors increased during lockdown whatever the characteristics of companies ($p < 0.05$ for stress levels before vs. first lockdown, for each variable), except for companies without employee ($n = 10$, 4.9 ± 2.8 vs. 4.8 ± 2.9, $p = 0.57$). Levels of stress remained significantly high after the lockdown except for the IT sector (6.8 ± 2.2 vs. 6.1 ± 2.0, $p = 0.08$) and companies up to 250 employees (6.3 ± 2.8 vs. 5.7 ± 2.7, $p = 0.05$). There was no significant decrease in stress after lockdown for retail trade, medical, nursing homes, pharmacies, restaurants, and accommodation sectors. Similarly, the percentage of directors with a stress > 8/10 increased with lockdown for all companies ($p < 0.05$), except for companies without employee, and for restaurants and accommodation sectors. After lockdown, the percentage of directors with a stress > 8/10 did not decrease except for construction and wholesale trade, and even increased for the accommodation sector (25.0% after vs. 14.8% during). Whatever the working status (continued or stopped) or the location (metropolis or countryside), the stress levels and the percentage of directors with stress > 8/10 increased significantly during lockdown ($p < 0.001$) without difference between groups (continued vs. stopped, or metropolis vs. countryside) (Figures 2, 3; Appendix 2).

		Stress of company directors VAS Mean ± sd			Time effect			Changes between groups during lockdown
		Before lockdown	During lockdown	After lockdown	During vs Before	After vs Before	After vs During	
Global	**807**	**5.4 ± 2.3**	**6.8 ± 2.6**	**6.5 ± 2.4**	***	***	***	
Company Size								
0 employee	10	4.9 ± 2.8	4.8 ± 2.9	4.7 ± 2.9	-	-	-	
1 to 9 employees	516	5.3 ± 2.4	6.7 ± 2.6	6.4 ± 2.5	***	***	**	
10 to 249 employees	265	5.5 ± 2.0	7.1 ± 2.3	6.8 ± 2.1	***	***	***	"0 employee"
10-49 employees	194	5.5 ± 2.0	7.2 ± 2.3	6.8 ± 2.2	***	***	**	< "1 to 9" and
50-99 employees	41	5.5 ± 2.1	7.0 ± 2.5	6.7 ± 2.4	***	***	-	"10 to 249"
100-249 employees	30	5.5 ± 1.4	7.0 ± 1.9	6.3 ± 1.8	***	***	**	
≥ 250 employees	16	5.7 ± 2.7	7.1 ± 2.6	6.3 ± 2.8	***	-	*	
Geographic location								
Metropolis	315	5.2 ± 2.2	6.6 ± 2.6	6.3 ± 2.4	***	***	**	-
Countryside	492	5.5 ± 2.3	6.9 ± 2.5	6.7 ± 2.4	***	***	**	-
Sectors								
Secondary sector	230	5.6 ± 2.0	7.1 ± 2.2	6.7 ± 2.1	***	***	***	-
Tertiary sector	576	5.3 ± 2.4	6.7 ± 2.7	6.5 ± 2.5	***	***	**	-
market	456	5.4 ± 2.3	6.8 ± 2.6	6.6 ± 2.5	***	***	**	-
non-market	120	4.9 ± 2.5	6.2 ± 2.9	6.0 ± 2.7	***	***	-	-
Most Represented Activities								
Construction trade	104	5.7 ± 2.1	7.3 ± 2.3	6.8 ± 2.2	***	***	**	-
Retail trade	85	5.3 ± 2.4	7.2 ± 2.5	6.8 ± 2.3	***	***	-	Retail > Other
Wholesale trade	55	5.4 ± 1.9	7.3 ± 2.3	6.5 ± 1.9	***	***	**	Wholesale > Other
Other Activities								
Health sector	47	4.9 ± 2.8	6.9 ± 2.9	6.4 ± 2.9	***	***	-	
Medical	35	4.8 ± 2.8	6.7 ± 2.9	6.3 ± 2.9	***	***	-	-
Nursing homes	10	5.7 ± 1.7	8.3 ± 1.5	7.7 ± 1.6	***	***	-	Nursing homes > Other
Pharmacies	12	5.0 ± 2.7	7.4 ± 3.2	6.7 ± 3.0	***	***	-	-
Food stores	25	5.6 ± 1.8	7.5 ± 1.7	6.5 ± 2.1	***	**	***	-
IT activities	9	6.1 ± 2.0	7.8 ± 1.9	6.8 ± 2.2	***	-	**	-
Restaurants	38	5.4 ± 2.6	6.3 ± 3.1	6.6 ± 2.7	*	**	-	-
Accomodation	28	5.2 ± 2.5	6.6 ± 2.5	6.5 ± 2.8	**	**	-	-
Working status during lockdown								
Continued	398	5.3 ± 2.2	6.8 ± 2.6	6.5 ± 2.4	***	***	***	-
Stopped	407	5.4 ± 2.3	6.9 ± 2.5	6.6 ± 2.4	***	***	**	-

FIGURE 2
Stress of company directors. VAS, Visual Analog Scale; SD, Standard Deviation. ***$p < 0.001$. **$p < 0.01$. *$p < 0.05$. -: non significant.

3.3.2. Effect sizes for increase in stress during lockdown

Sectors which had the biggest increase in stress levels during lockdown were retail trade (ES = 0.22, 95 CI 0.00 to 0.45), wholesale trade (0.26, 0.00 to 0.53) and nursing homes (0.55, −0.10 to 1.18). For pharmacies, this difference is at the limit of significance (0.47, −0.10 to 1.04). Biggest companies had the highest increase in stress levels (≥ 250 employees: 1.20, 0.36 to 2.03 vs. no employee; 10 to 249 employees: 0.90, 0.27 to 1.54; one to nine employees: 0.65, 0.03 to 1.28; vs. no employee). Geographical location and working status did not influence the increase of stress levels (Figure 4; Appendix 3).

3.3.3. Odds ratio

Sectors the most at risk of stress > 8/10 during lockdown tended to be nursing homes (OR = 2.52, 95 CI 0.73 to 8.82), pharmacies (2.54, 0.81 to 7.95), and IT activities (3.17, 0.84 to 11.90). Conversely, accommodations sector tended to have a lower risk of stress > 8/10 during lockdown (0.42, 0.15 to 1.24) followed by an increase after lockdown (25.0% after vs. 14.8% during). Biggest companies tended to have a higher risk of stress > 8/10 during the lockdown (≥ 250 employees: 5.40, 0.54 to 53.9; 10 to 249 employees: 4.18, 0.52 to 33.5; 1 to 9 employees: 3.36, 0.42 to 26.8; vs. no employee). Geographical location (metropolis vs. countryside) and working status (continued vs. stopped) did not influence the risk of stress > 8/10 (Figure 5; Appendix 4).

4. Discussion

The main findings were an increase of 26% in the stress of company directors during the first lockdown of the COVID-19 pandemic, and a four-time increase in the percentage of stress >

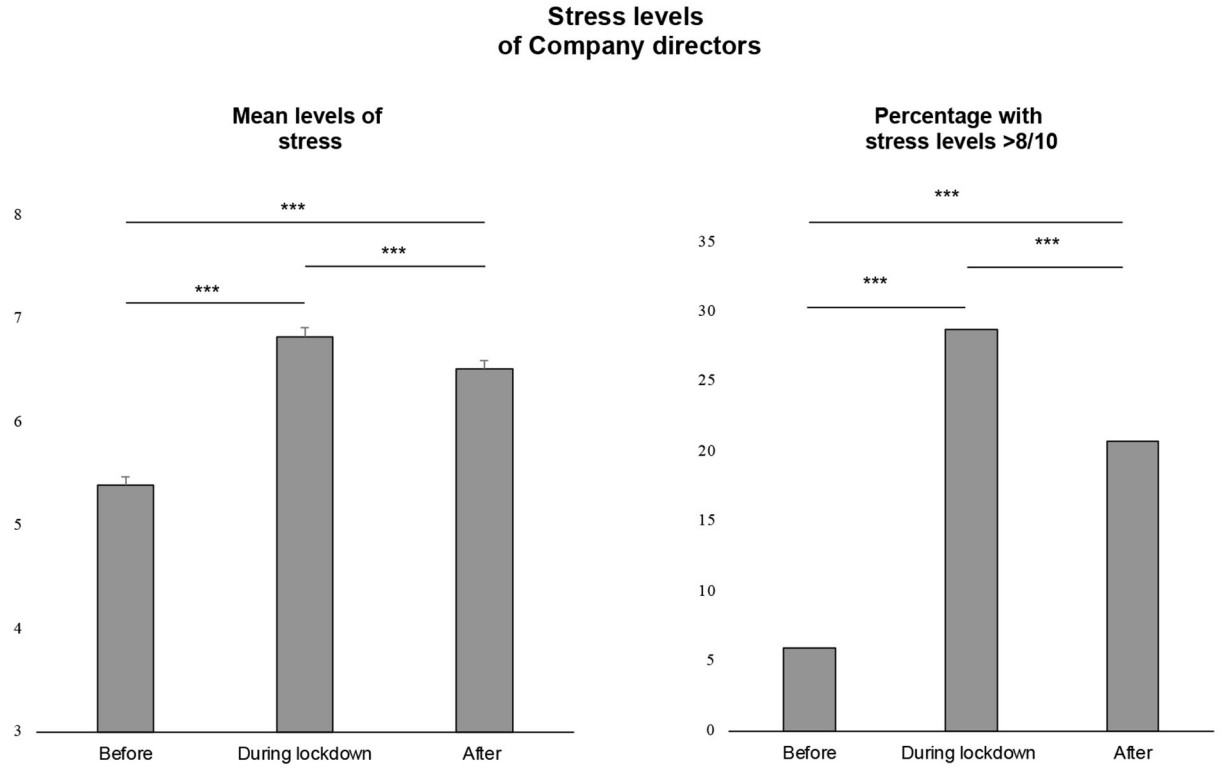

FIGURE 3
Stress levels of company directors (mean levels ± standard error of the mean and percentage with stress levels >8/10). ***: significant changes between periods ($p < 0.001$).

8/10 (intervention threshold). Medical and IT sectors were the most at-risk, as well as biggest companies.

4.1. Stress of company directors

This study demonstrated a 26% increase in stress levels of company directors, which seems higher than a 22% increase in stress levels of a general international population–also measured using visual analog scale (21). It also showed that nearly one third (29%) of company directors were at high levels of stress (> 8/10) during the lockdown. Even if threshold for high levels of stress may vary between studies, company directors seemed more at risk than prevalence of high levels of stress reported in other studies in general population: 12% in India (22), 5 and 8% in China (23), and 10% in Australia (24). Only one study reported stress levels of managers during the lockdown (25) and found lower prevalence than in the studied population. However, this study is the first study focusing specifically on the stress of company directors and reported the evolution of stress before, during, and after the first lockdown. The few studies assessing mental health of company directors during the COVID-19 pandemic were mainly not on stress but on anxiety (9), depression (9), and burnout (11), and none assessed the evolution of stress over three key periods of the pandemics. but only one assessed stress at work (12). We demonstrated a massive increase of stress of company directors. Results could be explained by the accumulation among company directors of numerous stress factors described in the literature such as gender, age, and relative income, although not assessed in our study (26, 27). It has been accentuated by the pandemic and lockdown. Indeed, they had been exposed to an overload of work and emotional requirements but also to insecurity at work (28) with difficulty in anticipating and a lack of autonomy in the face of government directives (29). Company directors had assumed strong responsibilities, including the risk of transmission of COVID-19 and the survival of their companies considering the economic difficulties (30). In addition, the stress levels of company directors before the pandemic (5.4 ± 2.3) were also superior to levels of other workers found in the literature: 4.0 ± 2.4 in French workers (20), 4.0 ± 2.7 in hospital workers (31), or 4.4 ± 2.1 managers/engineers (17), suggesting that company directors could be particularly exposed to stress like emergency health care workers (32, 33). Lastly, the stress of company managers remained high after the end of lockdown, showing

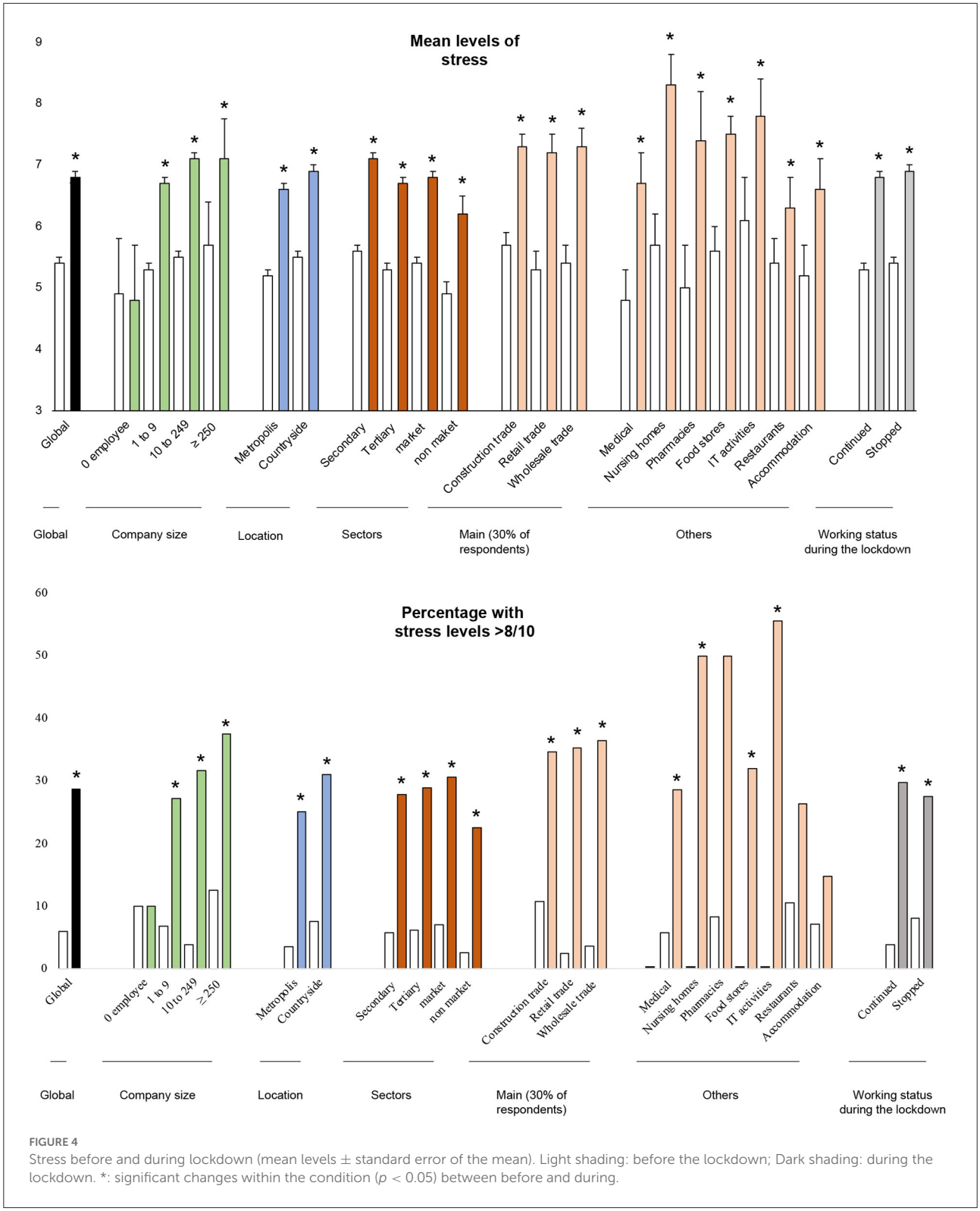

FIGURE 4
Stress before and during lockdown (mean levels ± standard error of the mean). Light shading: before the lockdown; Dark shading: during the lockdown. *: significant changes within the condition ($p < 0.05$) between before and during.

the need for action to be taken by the occupational health services. Despite specific preventive strategies are needed toward the mental health of company managers, it may be difficult for company directors to reduce their stressors, especially following the massive economic impact of a global pandemic. Some authors suggested recovery strategies allowing detachment from

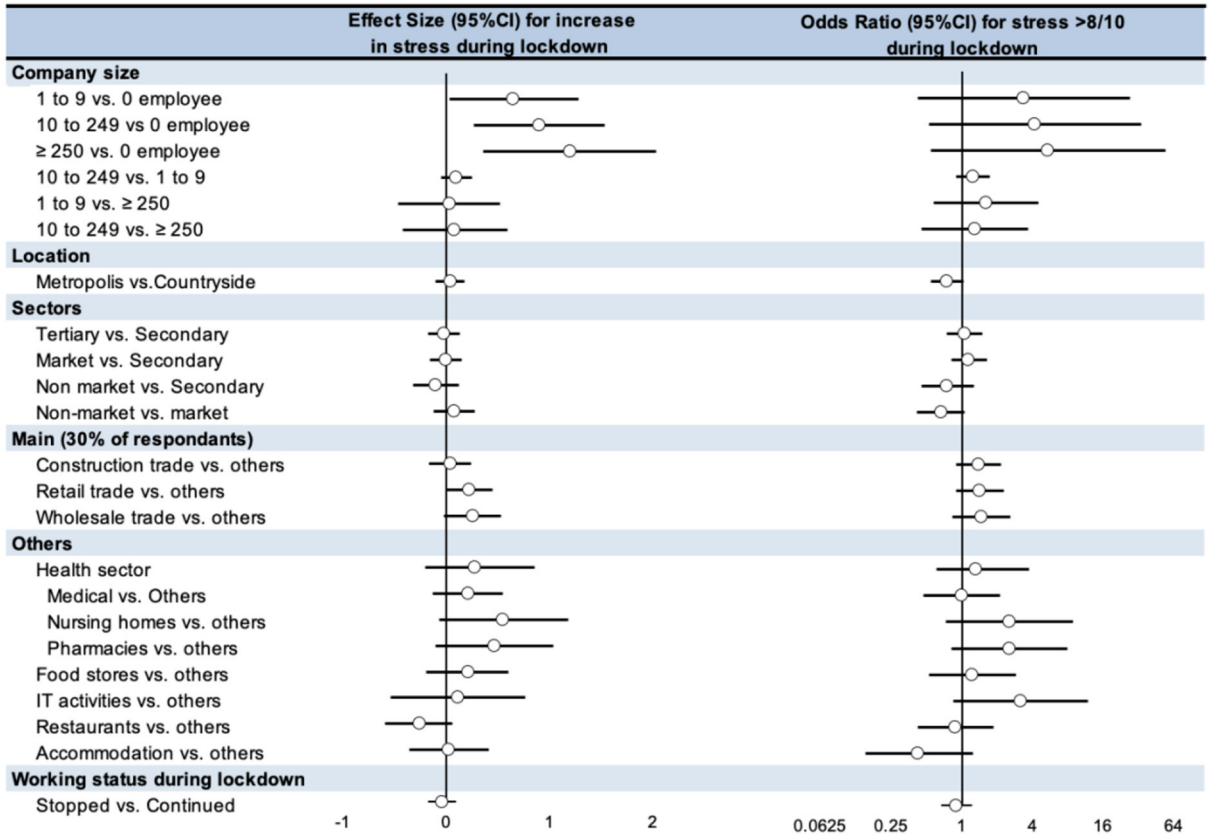

FIGURE 5
Factors influencing the increase in stress levels and risk for stress >8/10 (Odds Ratio) during lockdown. 95%CI, 95% Confidence Interval.

work stressors in non-work time and advise entrepreneurs to engage in absorbing recovery activities (e.g., physical exercise, meditation, socializing) (34). However, the need for more research to better understand the unique work situation of company directors is needed. Such studies should account for several levels of analyses (within-person and between-person effects) and time perspectives (short-term, mid-term, and long-term) (34).

4.2. Characteristics of companies at risk of stress

The novelty of our study laid in the impact of economic sectors on stress levels of company directors during the COVID-19 pandemic. While other studies on mental health of company directors during the pandemic were more precise for sociodemographic (9–11), none evaluated the sectors of economic activity the most at-risk. Despite the global lockdown massively impacted economy (13, 14), some sectors completely stopped their activity while some other sectors were under pressure. Our study showed a higher stress and/or a trend for more severe stress for certain sectors, such as medical and IT sectors. The stress of directors of nursing homes can be explained by the high job demand and emotional overload due to the fear of the risk of contamination and the management of suffering. Indeed, health workers in charge of COVID patients are described as being at high risk of psychological consequences (35), notably in a population of nursing homes health care workers (36). Those results also showed a trend toward higher and more severe stress for the IT sector, that experienced a significant work overload due to the advent of teleworking (37) and the need to implement digital and technological tools (38). Retail and wholesale trade had also high levels of stress during lockdown, facing a huge demand (14). For the restaurant and accommodation sectors, results showed a trend toward lower stress. These two sectors have been forced to close. Being forced to close can also be extremely stressful but the impact on stress of company directors may depend from stringency of governmental lockdown and from economic public measures (9). After lockdown, the stress decreased except for the nursing homes that were still exposed, and for restaurants and accommodations for which the absence of a return to activity led to economic difficulties. Directors of large companies

were more at risk of stress than directors of companies without employees. Indeed, the stress risk factors for directors differ according to the size of the company (39), particularly in terms of decision-making latitude, complexity of managing organizational change and economic survival. However, very limited literature have been published on this subject. This study did not show any difference in stress according to the location of the company, metropolis vs. countryside, which is coherent considering that the governmental directives were the same. Identifying companies the most at-risk is a necessary step to further build efficient preventive strategy (16).

4.3. Limitations

This study had some limitations. First of all, the sample was obtained through a voluntary online questionnaire, a method which leads to a non-response bias (40). However, despite a low response rate, we still collected an interesting sample of more than 800 company directors. In our study, this could induce a risk of non-representativity of our sample. Indeed, we had an important response rate of construction firms but a low response rate of health firms. This could be explained by the fact that directors of those firms were overwhelmed even more than usual during the lockdown contrary to the directors of constructions firms that were forced to stop all activities. The low sample in each category did not allow the odds ratio to be significant by company size and sector of activity, but we were able to differentiate several more at-risk sectors. Similarly, the effect sizes for the variation in stress during lockdown by sector of activity remained small or moderate (between 0.20 and 0.55). However, effect sizes are recommended when data are numerous to prevent from false significant findings, and we also acknowledge that none of previous studies on mental health of company directors reported effect sizes (9–11). The small sample sizes also did not allow for correlations between business activity levels over the different time periods studied and the variation in stress. Furthermore, the questionnaire was not exhaustive. Gender, age, and entrepreneurial experience of respondents were not asked to preserve anonymity. Those factors have been described as factors influencing stress (15, 41), particularly for age in a study conducted in a manager population during the COVID-19 pandemic (25). Our study also did not question the directors about the economic impact that lockdown and the pandemic may have had on their companies, that could also be stress confounders (30), such as for workload (42). In addition, 807 companies were selected solely from the population of a regional occupational health service, with no primary sector and very few large companies. Further studies should be conducted with a larger sample including primary sector and large companies on several geographical sites for generalizability. Future studies should also investigate more deeply psychosocial risk factors than we did with our single measure of stress using a single item. For example, using complementary validated questionnaires such as job-demand-control-support or effort-reward-imbalance models (41) may offer the possibility to build efficient preventive strategy, using predictive models (43, 44). Our study may have practical implications considering the putative very long-term (several years) impact of the pandemic on mental health, as we demonstrated on other population during the SARS-CoV-1 epidemic in 2003 (45).

5. Conclusions

The first lockdown of the COVID-19 pandemic had a major impact on the stress levels of company directors, which increased by 25.9% during lockdown. This study also demonstrated that almost a third of company directors (29%) had very high levels of stress (>8/10) during the first lockdown of COVID-19, requiring urgent action because of the risk of burnout, anxiety and depression. Furthermore, this rate was still higher after the lockdown (20.7%) compared to before lockdown (5.9%). Medical and IT sectors were particularly at risk, as well as directors of large companies. Future studies with larger sample are needed to be able to target occupational health actions among company directors the most at risk of stress. Qualitative interviews can be interesting to target precisely a potential psychosocial action. It could also be interesting to provide some longitudinal follow-up during the next months and years to assess the long-term impact of COVID-19 and lockdown.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The study was approved by the Ethics Committee (CPP Sud-Est VI Clermont-Ferrand) and registered on ClinicalTrials.gov number NCT04308187. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization: CJ, MC, FD, and J-BB-M. Methodology: FD, MC, and J-BB-M. Formal analysis: CL, FD, and MC. Investigation: FD and CJ. Writing—original draft preparation, supervision, and project administration: FD. Writing—review and editing: UU, JS, GV, CL, AV, and J-BB-M. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.975953/full#supplementary-material

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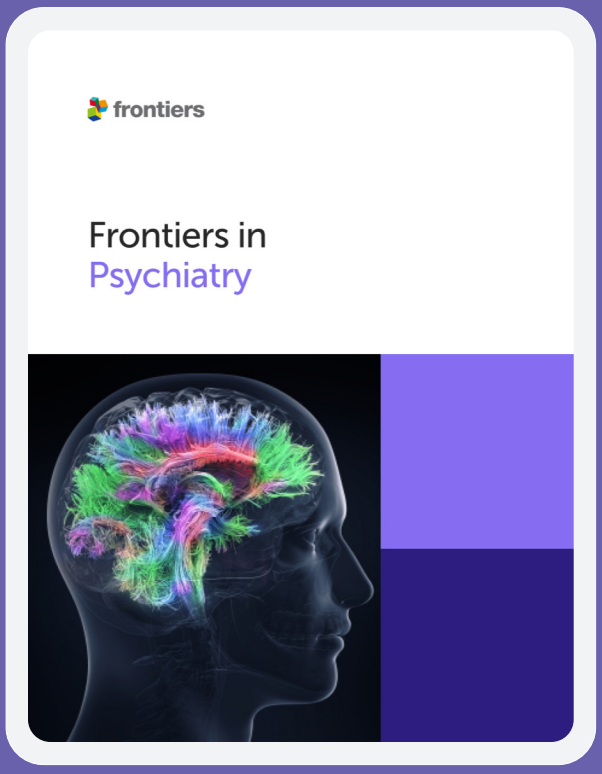

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