Journal of Primary Care & Community Health
Volume 12: 1–8

DOI: 10.1177/21501327211027432
journals.sagepub.com/home/jpc
SAGE

Mental Stress, Anxiety and Depressive Symptoms and Interleuken-6 Level among Healthcare Workers during the COVID-19 Pandemic

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Abstract

Objectives: This study aimed to evaluate the interleukin-6 (IL-6) levels and its relationship to stress, anxiety, and depressive symptoms among healthcare workers (HCWs) compared to controls during the COVID-19 pandemic. **Methods:** A total of 80 HCWs in Suez Canal University Hospital in Ismailia, Egypt, and 80 controls were analyzed during the COVID-19 pandemic. The Depression, Anxiety and Stress Scale (DASS 21) questionnaire was used, and serum IL-6 level was determined in both groups. **Results:** IL-6 levels were high in 81.2% (65) of HCWs compared to 36% (45) of controls ($P < .05$). The DASS score was higher in participants with high IL-6 levels (>3 ng/mL) than in those with mild to moderate levels ($P < .05$). The regression model revealed that the type of work as a healthcare staff, irregular or night shift, and stress were predictors of increased IL-6 levels among the studied sample ($P < .05$) (odds ratio = 20.30, 2.44, and 2.04, respectively). **Conclusion:** The IL-6 level and DASS score were higher in HCWs compared to those in controls during the COVID-19 pandemic. The type of work as a healthcare staff, stress, and irregular or night shift were predictors of increased IL-6 levels.

Keywords

mental stress, the COVID-19, IL-6, shift, anxiety, depression

Dates received 6 April 2021; revised 5 June 2021; accepted 6 June 2021.

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by enveloped, positive-stranded RNA viruses and was first identified in Wuhan City in December 2019, causing a cluster of pneumonia cases. It subsequently spread throughout China and then universally, becoming a global health emergency. In February 2020, the World Health Organization (WHO) nominated coronavirus disease 2019 as COVID-19.[1]

As of April 5, COVID-19 has spread to 198 countries, infecting >130 422 190 individuals and causing 2 842 135 deaths worldwide, and therefore considered a global pandemic.[2] Healthcare workers (HCWs) were subjected to high risks and stressors, both physical and psychological, which have potentially led to posttraumatic stress disorder (PTSD).[3]

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HCWs were vulnerable, due to the risk of getting infected particularly with inadequate resources. While their fundamental "duty to treat" was antagonistic to their hope to keep their families and loved ones away from further transmission of infection.[4]

The prevalence of depression, anxiety, insomnia and distress symptoms was assessed on a hospital-based survey study achieved in Wuhan among frontline HCWs from January 29, 2020, to February 3, 2020. The findings revealed high prevalence of depressive symptoms (50.4%), anxiety symptoms (44.6%), frequent insomnia (34.0%), and overall distress (71.5%) among HCWs.[5]

Psychological stresses were associated with the physiological response such as changes in immunological response and inflammation. Anxiety and depression contribute to increased risk for disorders with an inflammatory etiology, and elevated inflammatory activity may be a significant moderator of emotion-disease interactions.[6]

The reaction of circulating inflammatory cytokines to stress is associated with depression, previous stress exposure and cancer history. Many previous studies have examined the associations between depression and inflammation.[6,7]

Leukocytes, bone marrow cells and hepatocytes secrete a wide range of inflammatory cytokines. Numerous inflammatory cytokines react to the acute stress challenge, including interleukin IL-6, IL-10, IL-1 beta, and tumor necrosis factor (TNF)-α.[6]

IL-6 is produced by nearly all stromal and immune cells, such as B lymphocytes, T lymphocytes, macrophages, dendritic cells, monocytes, mast cells, fibroblasts, and endothelial cells. IL-1-β and TNF-α are the main stimulators of the IL-6 expression. Several other factors can contribute to its secretion such as Toll-like receptors, prostaglandins, adipokines, stress response and other cytokines.[8]

IL-6 acts through diverse signal transduction pathways[5] and combines to trans-membrane and a soluble form of its receptor IL-6R. Then this complex binds to gp130 triggering gene expression of the classical pathway. The JAK-STAT, RAS-RAF, and other pathways are activated, promoting cellular proliferation, differentiation, oxidative stress, and immune regulation.[9]

O'Donovan et al suggested that clinically anxious individuals have lower morning cortisol and elevated IL-6 levels compared with non-anxious individuals, highlighting a potential pathway by which anxiety may increase risk of inflammatory diseases, and found a relationship between negative emotions and biological responses.[10]

An essential constituent of public health measures for addressing the COVID-19 epidemic is protecting HCWs. Distinctive interventions to support the mental well-being in HCWs exposed to COVID-19 need to be immediately implemented with frontline HCWs demanding specific consideration.

Patients and Methods

This study aimed to assess IL-6 levels among HCWs during the COVID-19 pandemic in comparison to controls, measure stress, anxiety and depression and its ranks, and determine factors that predict IL-6 levels among HCWs and controls.

Eighty HCWs, includes 62 nurses and 18 laboratory and radiology technicians in Suez Canal University Hospital; Ismailia, Egypt, were included in a comparative cross -sectional study, from March 2020 to August 2020 during the COVID-19 pandemic.

Sixteen (20%) participants worked in the laboratory and blood bank; 30 (37%) in internal medicine, surgery and pediatrics departments, and 34 (42.5%) in the intensive care unit (ICU) and emergency department. Another 80 controls of staff relatives (not HCWs) were included in the study. All participants in both groups were asked to fulfill a questionnaire, and serum IL-6 level was assessed.

The questionnaire included sociodemographic data (age, sex, marital status, residence and educational level), job data (job, place of work, work duration in hours, work days per week), and characteristic of night shift if present (periodicity, number per month and duration). Depression, Anxiety and Stress Scale (DASS 21) Arabic version questionnaire was used,[11] which is a quantitative measure of distress along 3 axes of depression, anxiety and stress that can be a useful measure of disturbance, but it is not a categorical measure of clinical diagnosis, although it is clinically helpful to have tags to state the grade of severity relative to the population. The following cutoff scores have been developed to determine mild/moderate/severe/extremely severe scores for DASS 21, regarding depression score(normal, 0-4; mild, 5–6; moderate, 7–10; severe, 11–13; extremely severe, +14), anxiety score (normal, 0–3; mild, 4–5; moderate, 6–7; severe, 8–9; extremely severe, +10), and stress score (normal, 0–7; mild, 8–9; moderate, 10–12; severe, 13–16; extremely severe, +17).

IL-6 Level Determination by Enzyme-linked Immunosorbent Assay

Serum samples for IL-6 was drawn into EDTA tubes, spun immediately at 3000 g at 4°C for 20 minutes, and then frozen at −70°C for further analysis. Then, IL-6 levels were measured in batched samples with the enzyme-linked immunosorbent assay (ELISA) utilizing monoclonal antibodies to IL-6. With a high-sensitivity Human IL-6 ELISA kit (Chongqing Biospes Co., Ltd, China), the IL-6 ELISA was accomplished according to the manufacturer's instructions. All samples from all participants were assayed within the same assay plate. The standard curve was generated as per experiment. High and low concentration cytokine quality controls that included IL-6 were run on each plate.

Table 1. Sociodemographic Characteristics, Work Shift, IL-6 Level and Mental Symptoms among HCWs and Controls (n = 160).

	HCWs (n = 80)	Controls (n = 80)	*P*-value[¥]
Residence			
Urban	38 (47.5)	35 (43.8)	.63
Rural	42 (52.5)	45 (56.2)	
Sex			
Male	56 (70.0)	57 (71.2)	.86
Female	24 (30.0)	23 (28.8)	
Smoking			
Smoker	62 (77.6)	56 (70.0)	.42
Non-smokers	18 (22.5)	24 (30.0)	
Marital status			
Single	34 (42.5)	40 (50.0)	.42
Married	46 (57.5)	40 (50.0)	
Work shift			
Day	0 (0.00)	75 (93.8)	.01*
Night	36 (45.0)	0 (0.0)	
Day and night	44 (55.0)	5 (6.2)	
DASS			
Stress subscale	9.10 ± 4.15	6.83 ± 2.68	.01*,†
Anxiety subscale	6.63 ± 4.31	4.17 ± 3.09	.01*,†
Depression subscale	6.95 ± 4.67	4.37 ± 3.17	.01*,†
Total DASS	22.68 ± 12.24	15.69 ± 8.14	.00*,†
Stress level			
Normal	32 (40.0)	50 (62.5)	.00*,¥
Mild/moderate	32 (40.0)	27 (33.8)	
Severe/extremely severe	30 (37.5)	11 (13.8)	
Anxiety level			
Normal	24 (30.0)	37 (46.2)	.00*,¥
Mild/moderate	26 (32.5)	37 (46.2)	
Severe/extremely severe	30 (37.5)	6 (7.5)	
Depression			
Normal	26 (32.5)	39 (48.8)	.00*,¥
Mild/moderate	32 (39.5)	35 (44.0)	
Severe/extremely severe	22 (27.5)	6 (7.5)	
IL-6 (ng/mL)	30.86 ± 25.06	16.10 ± 17.99	.00*,†
IL-6 level[#]			
Low	4 (5.0)	16 (20.0)	.00*,¥
Moderate	11 (13.8)	28 (35.0)	
High	65 (81.2)	36 (45.0)	

Data are presented as numbers (%) or mean ± SD.
*Statistically significant at 95% level of confidence.
†Mann–Whitney *U*-test.
¥Chi square test.
#Low: <0.3 ng/mL, moderate: 0.3 to 3 ng/mL, high: >3 ng/mL).

Statistics: All analyses were conducted using the SPSS for Windows statistical package, version 22.0. The distribution of variables was compared with the normal distribution by the Kolmogorov–Smirnov goodness-of-fit test. The differences between groups in nonparametric quantitative data were assessed using the Mann–Whitney *U*-test. Backward stepwise multiple linear regression analysis was conducted for factors affecting IL-6 level. The significance level was considered at <0.05.

Results

Table 1 shows the Sociodemographic charachteristics, work shift, IL-6 level and mental symptoms among HCWs and controls (n = 160): 80 HCWs and 80 controls, results reported that 22.5% (18) of HCWs, and 30% (24) of controls were smokers. Moreover, 55% (44) of HCWs have both night and day shifts, while 45% (36) have night shift only, while 93.8% of controls worked at day time and nearly 6% had both night

Table 2. Comparison of Sociodemographic Characteristics, Type of Work, Shift, DASS Score, and Mental Symptoms According to IL-6 Level (n = 160).

Characteristics	Low-to-moderate IL-6 level[#] (n = 59)	High IL-6 level (n = 101)	*P*-value[¥]
Residence			
Urban	33 (45.8)	40 (45.5)	.92
Rural	39 (54.2)	48 (54.5)	
Sex			
Male	55 (76.4)	58 (65.9)	.20
Female	17 (23.6)	30 (34.1)	
Smoking			
Smoker	51 (70.8)	67 (76.1)	.56
Non-smokers	21 (29.2)	21 (29.2)	
Marital status			
Single	36 (50)	38 (43.2)	.48
Married	36 (50)	50 (56.8)	
Type of work			
HCW	12 (16.7)	68 (77.3)	.00*
Non-HCW	60 (83.3)	20 (22.7)	
Work shift			
Day	56 (77.8)	19 (21.6)	.00*
Night	5 (6.9)	31 (35.2)	
Day and night	11 (15.3)	38 (43.2)	
DASS			
Stress subscale	6.07 ± 2.38	9.57 ± 3.72	.01*,†
Anxiety subscale	3.32 ± 2.44	7.25 ± 4.03	.01*,†
Depression subscale	3.64 ± 2.75	7.40 ± 4.42	.01*,†
Total DASS	13.03 ± 6.52	24.22 ± 11.27	.00*,†
Stress level			
Normal	57 (79.2)	25 (28.4)	.00*,¥
Mild/moderate	14 (19.5)	45 (51.1)	
Severe/extremely severe	1 (1.4)	18 (20.5)	
Anxiety level			
Normal	46 (63.9)	15 (17.0)	.00*,¥
Mild/moderate	23 (31.9)	40 (45.5)	
Severe/extremely severe	3 (4.2)	33 (37.5)	
Depression			
Normal	43 (59.7)	22 (25)	.00*,¥
Mild/moderate	26 (36.1)	41 (46.9)	
Severe/extremely severe	3 (4.2)	25 (28.4)	
IL-6 (ng/mL)	1.02 ± 1.37	34.86 ± 21.16	.00*,†

Data are presented as numbers (%) or mean ± SD.
*Statistically significant at 95% level of confidence.
†Mann–Whitney test.
¥Chi square test.
#Low: <0.3 ng/mL, moderate: 0.3 to 3 ng/mL, high: >3 ng/mL.

and day shifts. For HCWs, the night shift work duration was 9.93 ± 2.14. The results demonstrated IL-6 levels, where 81.2% (65) of HCWs exhibited high levels compared to 20% (16) of controls ($P < .05$). Furthermore, 37.5% (30) of HCWs reported severe to extremely severe stress compared to 13.8% (11) of controls ($P < .05$). Regarding symptoms of anxiety, 37.5% (30) and 7.5% (6) of HCWs and controls respectively reported severe to extremely severe symptoms ($P < .05$). Moreover, 22% (27.5) and 7.5% (6) of HCWs and controls respectively reported severe to extremely severe depressive symptoms ($P < .05$). The results reported that the mean IL-6 level was 30.86 ± 25.06 ng/mL in HCWs compared to 16.10 ± 17.99 ng/mL in controls ($P < .05$).

Table 2 shows the Sociodemographic characteristics, work shift, IL-6 level and mental symptoms between participants with low (0.3 ng/mL to moderate (0.3-3 ng/mL)

Table 3. Logistic Regression of IL-6 Level According to Study Covariates in All Studied Sample (Model-A) and among HCWs (Model B).

	Model A	
Predictors	OR (95% CI)	*P*-value
Constant	0.14	.00*
Work type **(HCWs vs controls)**	20.30 (7.30-56.45)	.00*
Day shift vs **(night and day or night only)**	2.44 (1.37-4.33)	.00*
Stress level (normal, mild to moderate and severe)	2.04 (0.94-4.46)	.03*
	Model B	
Predictors	OR (95% CI)	*P*-value
Constant	0.124	.04*
Night shift **vs** irregular (night and day)	4.49 (1.40-35.80)	.00*
Stress level (normal, mild to moderate and severe)	10.98 (2.53-27.63)	.00*

*Statistically significant at 95% level of confidence.
IL-6 (Low/moderate and high). Predictors: work type, shift, stress, depression and anxiety, sex, age and smoking.

IL-6 levels (n = 59) and those with high levels (n = 101) (>3 ng/mL). The results showed no statistically significant difference in sex, residence, marital status and smoking between groups ($P > .05$). The results presented that 83.3% (60) and 16.7% (12) of HCWs and controls respectively reported normal to moderate IL-6 levels, while 77.3% (68) and 22.7% (20), respectively had high levels ($P < .05$). Approximately 79% (57) of participants with low/moderate IL-6 levels had normal stress, and 1.4% (1) reported severe to extremely severe stress compared to 28.4% (25) and 20.5% (18) of participants with high IL-6 levels respectively ($P < .05$). Regarding symptoms of anxiety; 63.9% (46) and 17% (15) of the low/moderate IL-6 level and high IL-6 level groups, had normal anxiety level respectively, while 37.5% (33) and 4.2% (3), respectively, reported severe to extremely severe symptoms ($P < .05$). Approximately 59.7% (43) of participants with low to moderate IL-6 levels and 25% (22) of participants with high IL-6 levels showed normal depressive symptoms, while 4.2% (3) and 28.4% (25) respectively reported severe to extremely severe depressive symptoms ($P < .05$).

Table 3 model–A shows the logistic regression analysis among all studied participants where work type (HCWs, controls), anxiety, depression, stress (normal, mild/moderate, severe/extremely sever), shift type (day shift vs (night and day or night only)), sex, age, and smoking were independent variables (predictors) and IL-6 level(low/moderate and high) was dependent variable. The model revealed that HCWs as a type of work, night or day and night shift, and stress were predictors of high IL-6 levels among the studied sample ($P < .05$) (Odds ratio [OR] = 20.30, 2.44, and 2.04 respectively). Model-B summarizes the logistic regression analysis among HCWs where anxiety, depression, stress (normal, mild/moderate, severe/extremely severe), shift type (night shift vs irregular shift (night and day)), sex, age and smoking were independent variables (predictors) and IL-6 level(low/moderate and high) was a dependent, the model revealed that night shift and stress were predictors of high IL-6 level ($P < .05$) (OR = 4.49, 10.98).

Discussion

Since the WHO has declared COVID-19 as a pandemic, HCWs were on the battle zone, dealing directly with COVID-19 patients, involved in examination, the diagnosis, and caring of COVID-19 these patients and being at a higher risk for COVID-19 infection, HCWs are at higher risk for developing psychological distress and mental health problems.[12-14] In our study, about two-thirds of HCWs reported variable levels of anxiety, depression, and stress symptoms (70%, 67.5%, and 60%, respectively) compared to control group.

A survey conducted in Saudi Arabia by Temsah et al[15] included 44.8% responses from critical care departments (ICU and emergency) HCWs were susceptible to various health consequences due to the COVID-19 pandemic. Several risk factors were identified; long duty hours, and working in the high-risk department were well-identified risk factors which were in agreement with our study results.

Our study findings were consistent with the results of numerous studies that were performed during the COVID-19 pandemic and indicated a global rise in the prevalence of psychological outcomes among HCWs. In a Chinese study on 493 physicians and 764 nurses, 50.4% had depressive symptoms, 44.6% had anxiety symptoms, and 71.5% reported overall distress. With further analyses, Lai's study showed that nurses had more severe levels of psychological distress symptoms compared to other HCWs 5. In another

multicenter Chinese study on 1563 medical staff, the prevalence of depression was 50.7%, that of anxiety was 44.7%, and that of stress-related symptoms was 73.4%.[16] Conversely, during the earlier severe acute respiratory syndrome outbreak (2002-2004), 89% of HCWs reported psychological distress symptoms.[17] However, the prevalence of anxiety, depression, and stress symptoms among HCWs in our study was substantially higher than those of other studies during the COVID-19 pandemic. For example, a study including 680 medical doctors and 247 nurses reported a prevalence of 13% and 12.2% for anxiety and depression, respectively.[14] Another Chinese study including 1173 frontline HCWs reported that 15.7% had anxiety symptoms and 14.3% had depressed mood while 52.6% had mental health problems.[18]

The high prevalence of psychological problems among HCWs, particularly during public health emergencies such as the COVID-19 pandemic, could be explained by their safety concerns while working, long working hours, irregular shift work, highly demanding work, poor psychosocial work environment, and frequent exposure to serious life circumstances.[5,14] Safety concerns among HCWs arise from the insufficient understanding of the virus, lack of effective preventive and control measures, increased risk of infection due to exposure to high viral load while dealing with patients with COVID-19, and the shortage in the medical protective equipment.[14,19,20] On the contrary, the high prevalence of stress and anxiety symptoms among the control group in our study may be contributed to the eminence of dread that is present globally during the COVID-19 pandemic.

Elevated levels of pro-inflammatory cytokines, such as IL-6, have been noted in the development of common mental health problems.[21] Therefore, we have examined the association between IL-6 and psychological distress symptoms (ie, depression, anxiety, and stress) among the studied sample of nurses. The majority of HCWs (81.2%) in our sample had a higher IL-6 level (>3.0 ng/mL) with a mean (±SD) of 31 (±25) ng/mL compared to the control group (25%). Besides, although female nurses constituted only 30% HCWs, they had significantly higher IL-6 level than male nurses. Moreover, nurses engaged in continuous night shifts had significantly higher IL-6 levels than nurses on alternating work shifts and both higher than controls who worked at daytime only.

Then, the high IL-6 levels in our sample could be explained partially by night shift work, and the sex-difference in IL-6 level was related to stress response. Earlier studies involving IL-6 level measurement support this observation. In a Japanese study on 5259 workers, the association between work schedule and IL-6 was examined. The findings reported that the night workers had significantly higher levels of log-transformed IL-6 compared to those with regular work schedules, even after adjusting for sociodemographic and work-related factors, including job stress.[22] Circadian rhythm disruption and sleep deprivation were among the most common explanatory factors of increased IL-6 level among night workers.[23,24] Conversely, further studies demonstrated greater IL-6 stress responses in women.[25,26]

Furthermore, our study denoted that high IL-6 levels was significantly associated with increased depression, anxiety, and stress scores, with stress being the most common predictor of IL-6 levels among HCWs and among all participants including controls. Our results are consistent with those of former studies that investigated the association between IL-6 and mental health problems, particularly among HCWs. A Japanese study on133 female HCWs, the reported that elevated serum IL-6 levels was directly correlated with depressive symptoms.[27] Likewise, Bob et al[28] demonstrated a significant correlation between IL-6 and both depression and PTSD. A study by Virtanen et al[29] had further investigated the association between IL-6 level and the recovery from psychological distress symptoms in a non-clinical sample; low IL-6 at baseline was associated with substantial symptom resolution at follow-up.

Furthermore, Falco's study had investigated the association between serum IL-6 level and both job demands (JD) and job resources (JR) in 119 employees at an Italian healthcare organization. They concluded that exposure to stressful work situations (ie, high JD and low JR) is associated with higher IL-6 levels among HCWs,[30] which was consistent with current study results where being a healthcare staff was a predictor of increased serum IL-6 levels.

Some limitations should considered while interpreting our study findings. First, our study had a cross-sectional design in which causal inferences cannot be settled due to the lack of temporal relationship. A longitudinal study design should be considered in further research to further address the question of causal direction. Second, we used IL-6 level as a sole biomarker of inflammatory cytokines. Future studies should consider other inflammatory cytokines such as C-reactive protein and TNF-α. Finally, our conclusion was based on a single IL-6 measurement; however, serial measurements of IL-6 would further explain the relationship under study. Finally, the direct causal relationship between work-related factors, particularly details of night shift work, and IL-6 level was not well-characterized and warranted further investigation.

Conclusion

The IL-6 levels among studied HCWs (81.2%) were higher compared to controls. They reported increased stress, anxiety and depressive symptoms which correlated with IL-6 levels during the COVID-19 pandemic. The type of work as a HCW, stress and night shift were predictors of increased IL-6 levels.

Author Contributions

Shaimaa A. A. M. Amer[1]: idea of research, protocol writing, biostatistics, revision. Maha Anani[6]: IL-6 measurements, questionnaire collection. Ahmed Mahmoud Fouad, Mohamed El-Samahy: questionnaire collection, discussion. Asmaa A. Hashem, Abdullah A. saati, Anas A. Sarhan: writing introduction and methodology, revision. All authors reviewed, commented and approved the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Self-funded by authors.

Ethics

Approval from medical research committee of Faculty of Medicine, Suez Canal University was obtained (No. 4426, 22\7\2020) and complied with local legislation and the Declaration of Helsinki, and **informed consent** was obtained from each participant in the study.

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References

1. Centers of Disease Control and Prevention [Internet]. *Coronavirus Disease 2019 (COVID-19)*. Centers; 2020. Accessed August 6, 2020. https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html
2. World Health Organization [Internet]. *COVID-19 Situation Reports*. The Organization; 2021. Accessed April 5, 2021. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports#
3. Paladino L, Sharpe RP, Galwankar SC, et al. Reflections on the Ebola public health emergency of international concern, part 2: the unseen epidemic of posttraumatic stress among health-care personnel and survivors of the 2014–2016 Ebola outbreak. *J Glob Infect Dis*. 2017;9(2):45-50.
4. Thomas STL, Wai CY. The lessons of SARS in Hong Kong. *Clin Med*. 2010;10(1):50. doi:10.7861/clinmedicine.10-1-50
5. Lai J, Ma S, Wang Y, et al. factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019. *JAMA Netw Open*. 2020;3(3):e203976.
6. Marsland AL, Walsh C, Lockwood K, John-Henderson NA. The effects of acute psychological stress on circulating and stimulated inflammatory markers: a systematic review and meta-analysis. *Brain Behav Immun*. 2017;64:208-219.
7. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*. 2008;9(1):46-56. doi:10.1038/nrn2297
8. Jones SA, Jenkins BJ. Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer. *Nat Rev Immunol*. 2018;18(12):773-789. doi:10.1038/s41577-018-0066-7
9. Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. *Nat Immunol*. 2015;16(5):448-457.doi:10.1038/ni.3153
10. O'Donovan A, Hughes BM, Slavich GM, et al. Clinical anxiety, cortisol and interleukin-6: evidence for specificity in emotion–biology relationships. *Brain Behav Immun*. 2010;24(7):1074-1077.
11. Moussa MT, Lovibond PF, Laube R, Megahead AM. Psychometric properties of an Arabic version of the Depression Anxiety Stress Scales (DASS21). *Res Soc Work Pract*. 2017;27(3):375-386.
12. Preti E, Di Mattei V, Perego G, et al. The psychological impact of epidemic and pandemic outbreaks on healthcare workers: rapid review of the evidence. *Curr Psychiatry Rep*. 2020;22(8):43.
13. Serrano-Ripoll MJ, Meneses-Echavez JF, Ricci-Cabello I, et al. Impact of viral epidemic outbreaks on mental health of healthcare workers: a rapid systematic review and meta-analysis. *J Affect Disord*. 2020;277:347-357.
14. Zhang WR, Wang K, Yin L, et al. Mental health and psychosocial problems of medical health workers during the COVID-19 epidemic in China. *Psychother Psychosom*. 2020;89(4):242-250.
15. Temsah M-H, Al-Sohime F, Alamro N, et al. The psychological impact of COVID-19 pandemic on health care workers in a MERS-CoV endemic country. *J Infect Public Health*. 2020;13(6):877-882. doi:10.1016/j.jiph.2020.05.021
16. Liu S, Yang L, Zhang C, et al. Online mental health services in China during the COVID-19 outbreak. *Lancet Psychiatry*. 2020;7(4):e17-e18.
17. Chua SE, Cheung V, Cheung C, et al. Psychological effects of the SARS outbreak in Hong Kong on high-risk health care workers. *Can J Psychiatry*. 2004;49(6):391-393.
18. Cai Q, Feng H, Huang J, et al. The mental health of frontline and non-frontline medical workers during the coronavirus disease 2019 (COVID-19) outbreak in China: a case-control study. *J Affect Disord*. 2020;275:210-215. doi:10.1016/j.jad.2020.06.031
19. Lázaro-Pérez C, Martínez-López JÁ, Gómez-Galán J, López-Meneses E. Anxiety about the risk of death of their patients in health professionals in Spain: analysis at the peak of the COVID-19 pandemic. *Int J Environ Res Public Health*. 2020;17(16):5938.
20. Si M-Y, Su X-Y, Jiang Y, et al. Psychological impact of COVID-19 on medical care workers in China. *Infect Dis Poverty*. 2020;9(1):113.
21. Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. *J Affect Disord*. 2013;150(3):736-744.
22. Amano H, Fukuda Y, Yokoo T, Yamaoka K. Interleukin-6 level among shift and night workers in Japan: cross-sectional

analysis of the J-HOPE study. *J Atheroscler Thromb*. 2018; 25(12):1206-1214.
23. Rohleder N, Aringer M, Boentert M. Role of interleukin-6 in stress, sleep, and fatigue. *Ann N Y Acad Sci*. 2012;1261:88-96.
24. Reinhardt ÉL, Fernandes PACM, Markus RP, Fischer FM. Night work effects on salivary cytokines TNF, IL-1β and IL-6. *Chronobiol Int*. 2019;36(1):11-26.
25. Lockwood KG, Marsland AL, Cohen S, Gianaros PJ. Sex differences in the association between stressor-evoked interleukin-6 reactivity and C-reactive protein. *Brain Behav Immun*. 2016;58:173-180.
26. Panagi L, Poole L, Hackett RA, Steptoe A. Sex differences in interleukin-6 stress responses in people with type 2 diabetes. *Psychophysiology*. 2019;56(6):e13334.
27. Tsuboi H, Sakakibara H, Tatsumi A, et al. Serum IL-6 levels and oxidation rate of LDL cholesterol were related to depressive symptoms independent of omega-3 fatty acids among female hospital and nursing home workers in Japan. *J Affect Disord*. 2019;249:385-393.
28. Bob P, Raboch J, Maes M, et al. Depression, traumatic stress and interleukin-6. *J Affect Disord*. 2010;120(1-3):231-234.
29. Virtanen M, Shipley MJ, Batty GD, et al. Interleukin-6 as a predictor of symptom resolution in psychological distress: a cohort study. *Psychol Med*. 2015;45(10):2137-2144.
30. Falco A, Dal Corso L, Girardi D, De Carlo A, Comar M. The moderating role of job resources in the relationship between job demands and interleukin-6 in an Italian healthcare organization. *Res Nurs Health*. 2018;41(1):39-48.