



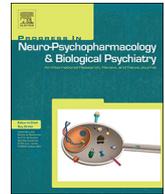
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## Psychiatric symptomatology associated with depression, anxiety, distress, and insomnia in health professionals working in patients affected by COVID-19: A systematic review with meta-analysis

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## ABSTRACT

**Background:** Health professionals are key personnel to containing infectious diseases like COVID-19. In the face of long work shifts (that reach 16 h per day on average), the risk of getting infected by a high-infectious disease and the lack of enough biological protection measures, mental suffering among health professionals suddenly became evident.

**Method:** We carried out an updated meta-analysis to investigate the psychiatric impacts on health professionals in the face of the physical and psychological conditions to which they are subjected due to the high demands of the COVID-19 pandemic. Papers were researched in four databases from December 2019 to April 2020. In total, eight papers were included in the study.

**Results:** Health professionals working to fight COVID-19 are being more severely affected by psychiatric disorders associated with depression, anxiety, distress and insomnia, stress, and indirect traumatization than other occupational groups. No significant differences were observed in the publication bias.

**Conclusion:** There is a strong association between health professionals and COVID-19 in terms of psychiatric repercussions. Our meta-analysis showed that health professionals have a higher level of indirect traumatization, in which the level of damage exceeds psychological and emotional tolerance and indirectly results in psychological abnormalities. The incidence of obsessive-compulsive traces and somatizations was higher in situations involving front-line professionals.

### 1. Introduction

At the end of December 2019, the first cases of pneumonia etiologically associated with a new virus, which was later identified as SARS-CoV-2, were registered in the city of Wuhan, province of Hubei, China. The new coronavirus disease (COVID-19) may create a variable clinical spectrum of symptoms and signs, which varies from asymptomatic conditions to the occurrence of a Severe Acute Respiratory Syndrome (SARS). Its spread has increased quickly. On January 20, China confirmed the transmission of COVID-19 from human to human. On January 23, the city of Wuhan closed all its access paths to decrease disease spread, but this was not enough. On January 30, 2020, during an emergency meeting convened by the World Health Organization (WHO), COVID-19 was pointed out as a public health emergency of international interest, and it was declared a pandemic on March 11, 2020 (Lai et al. 2020; Zhang et al. 2020). 2,719,897 cases of COVID-19

and 187,705 deaths have been confirmed in the world until April 25, 2020, according to an information report from the Pan American Health Organization – PAHO (2020) and WHO (2020).

China disclosed the adoption of active measures to help control the quick spread of COVID-19 in its territory. More than 30,000 health professionals moved to the province of Hubei and city of Wuhan. This professional category was soon affected by the SARS-CoV-2 spread. Since the beginning of the pandemic, more than 3000 health professionals were infected in China (Li et al. 2020; Huang and Zhao 2020a). In the face of long work shifts (that reach 16 h per day on average), the risk of getting infected by a high-infectious disease and the lack of enough biological protection measures, mental suffering among health professionals suddenly became evident and, as a consequence, it brought sleep, anxiety, and depression disorders. Thus, not only the physical health, but also the mental health of these workers became more vulnerable during the COVID-19 outbreak (Huang and Zhao

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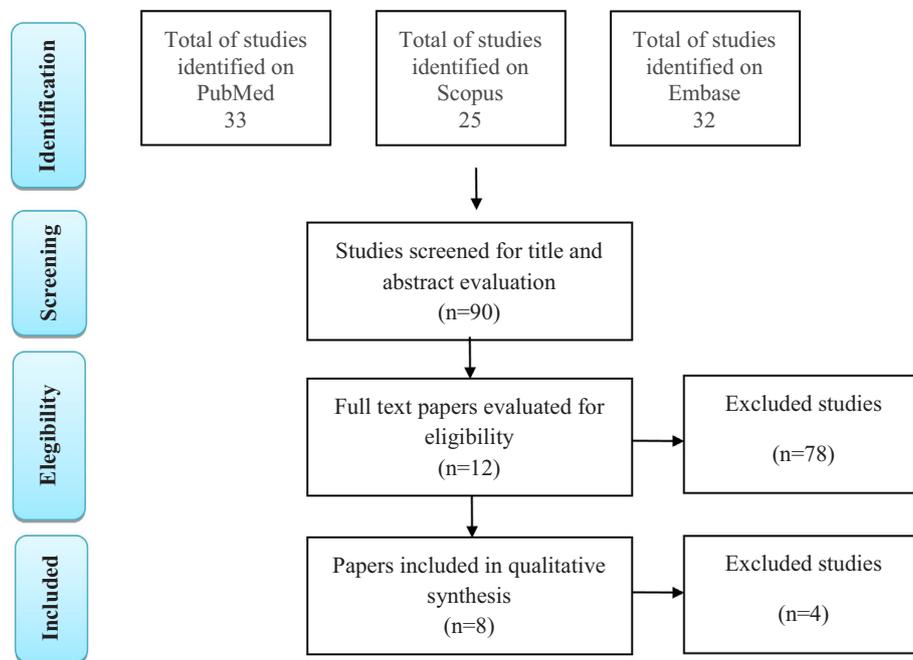


Fig. 1. Flowchart of literature search.

2020a, 2020b; Dai et al. 2020).

Hence, health professionals are key personnel to containing infectious diseases like COVID-19. They perform their activities in a full and assertive way when in a calm environment where the risks they are exposed to are dully controlled. Thus, more should be understood about the mental health condition of these workers and the negative psychological repercussions when facing a prolonged source of distress to plan actions that promote and protect their mental and physical health (Mo et al. 2020; Lai et al. 2020).

On February 2, 2020, the China State Council announced the adoption of direct lines of psychological support in the entire country to offer help during the pandemic (Lai et al. 2020). Such action was based on studies indicating that the authorities should provide effective information and guidance regarding personal protection and also psychological interventions that may safeguard the mental health of the entire population (Wang et al. 2020). Another study found that health education should be combined with psychological counseling for vulnerable subjects, such as the health professionals that are in the front-line fighting COVID-19 (Mo et al. 2020).

Based on a scenario of increasing pandemic threat and a global atmosphere of anxiety, along with depression caused by the social distancing measures recommended to reduce disease transmission and an overload of information disclosed by different media outlets, information collection on the behavior and mental condition of health workers may help establish effective measures that stimulate and protect their health during the war against the pandemic (Wang et al. 2020). Due to this situation, we have aimed to formulate a systematic review of literature regarding the psychiatric repercussions in health professionals that work in health systems to fight the clinical implications caused by COVID-19.

## 2. Method

### 2.1. Research strategy

A systematic research of all published papers was made in PubMed, Embase, ISI (Web of Science) and Scopus databases using the following combination of keywords: “COVID-19” OR “Coronavirus Infections” (Medical Subject Headings – [MeSH term]); “Health Personnel” OR

“Health Care Provider” [MeSH term]; and “Mental Health” (MeSH term), from December 2019 to April 2020.

The reason for limiting time to 2019–2020 was because during this period there was an increase in the number of research studies about health professionals as populations that are vulnerable to being contaminated by a highly virulent disease. Therefore, concern for health professionals has been associated not only with anxiety but also with other multiple clinical manifestations, like depression (having to face a large number of deaths, long work shifts and their association as an important indicator of psychic distress due to multiple uncertainties and demands associated with the treatment of COVID-19 patients).

The following searches were carried out: 1 and 2 and 3. The search strategy and retrieved papers were reviewed in two separate occasions to ensure proper sampling. Then, each paper from the sample was read and data were extracted and added to a matrix that authors, journal, study sample description and main conclusions.

### 2.2. Research guiding question

This study is based on the following research question: What are the psychiatric impacts on health professionals in the face of physical and psychological conditions to which they are subjected due to the high demands of the COVID-19 pandemic?

This question had obtained a larger impact in 2020 due to situations that involve health professionals directly in the diagnosis, treatment and support to COVID-19 patients, in the development of psychic spaces for pain installation and psychic suffering and other mental health symptoms. Thus, this systematic review aims to present the causes, psychiatric disorders per se, consequences and potential interventions.

### 2.3. Inclusion and exclusion criteria

The eligible studies should meet the following inclusion criteria: original studies about the psychiatric repercussions in health professionals involved in the fight against COVID-19; observational studies that measured the behavioral actions of health professionals involved in the fight against COVID-19. We excluded review studies and Controlled Randomized Trials, case reports, studies with methodological bias and conflicting results; there were no restrictions regarding language.

## 2.4. Data collection and results

Data were collected independently by two reviewers (MLRN and FCTS) and any divergences between reviewers were solved by a mediator until a consensus was reached. The remaining papers were researched in full to determine if they met the inclusion criteria or not. The necessary information was collected from published papers (Fig. 1).

## 2.5. Statistical analysis

Stata, version 14.0 (Stata Corp), was used to collect data and perform relevant analyses in this meta-analysis. Each numerical value of the result was presented with a 95% confidence interval (95%CI). The publication bias was found through the Egger and Begg tests,  $p < 0.05$  was considered a significant publication bias. In addition, a sensitivity analysis was performed to test result stability using Stata 12.0 software.

## 3. Results

### 3.1. Study characteristics

The detailed steps of the literature research flow and screening process were described in Fig. 1. A total of 90 papers were found. Two independent researchers analyzed the title and abstract of the paper, 78 studies were removed because they did not meet the inclusion criteria and 12 potentially related papers were eligible. In the end, eight papers were considered relevant for a systematic review with meta-analysis.

The papers included those by Zhang et al. (2020) – a study about the psychosocial problems of health professionals that are not doctors; Lai et al. (2020) – a study about factors associated with the mental health of health professionals; Li et al. (2020) – a study about stress as a psychological factor and indirect traumatization of professionals; Mo et al. (2020) – a study about stress among nurses; Qi et al. (2020) – a study about the mental stress of professionals; Huang and Zhao (2020a) – a study about the determination of health professionals as a high risk group; Huang and Zhang (2020b) – a study about the assessment of mental health burden of the Chinese; and Dai et al. (2020) – a study about the risk perception and immediate psychological condition of health professionals. The main characteristics of the chosen studies were summarized in Table 1.

### 3.2. Psychiatric repercussions and health professionals

As shown in Table 1, we found that the psychiatric repercussions among health professionals in the fight against COVID-19 was significant in studies developed in European and non-European countries. Results of a sensitivity analysis revealed that the studies significantly showed a posttraumatic stress concentration among professionals, which indicated statistically robust results. The publication bias was examined both in a qualitative (funnel plot asymmetry) and quantitative manner (Begg's test [ $z = 1.95, p = 0.342 > 0.05$ ] and Egger's test [ $t = 0.95, p = 0.352 > 0.10$ ]). In general, no publication bias evidence was observed.

Psychiatric repercussions in health professionals during the COVID-19 response were significant among the studies. For Zhang et al. (2020), health workers who are also doctors ( $n = 927$ ) showed a higher prevalence of insomnia (38.4 vs. 30.5%,  $p < 0.01$ ), anxiety (13.0 vs. 8.5%,  $p < 0.01$ ), depression (12.2 vs. 9.5%,  $p < 0.04$ ), somatization (1.6 vs. 0.4%;  $p < 0.01$ ) and obsessive-compulsive symptoms (5.3 vs. 2.2%;  $p < 0.01$ ) in comparison with health workers who are not doctors ( $n = 1255$ ). These health professionals need mental health attention and recovery programs. Lai et al. (2020) highlight that a considerable amount of the subjects reported depression symptoms (634 [50.4%]), anxiety (560 [44.6%]), insomnia (427 [34.0%]), and distress (899 [71.5%]). Li et al. (2020) have observed that the indirect traumatization scores for front-line nurses, including psychological scores and

responses, were significantly lower ( $p < 0.001$ ).

Mo et al. (2020) pointed out that the multiple regression analysis showed that children, work hours per week and anxiety were the main factors affecting the level of stress of nurses ( $p = 0.000, 0.048, 0.000$ , respectively). For Qi et al. (2020), a total of 1306 subjects were enrolled. A group of subjects had significantly higher scores of PSQI ( $p = 0.0001$ ), AIS ( $p < 0.0001$ ), anxiety ( $p < 0.0001$ ), and depression ( $p = 0.0010$ ) and a higher prevalence of sleep disorders with PSQI  $> 7$  points ( $p < 0.0001$ ) and AIS  $> 6$  points ( $p = 0.0001$ ). Huang and Zhao (2020a) pointed out that health professionals have a higher rate of sleep disorders in comparison with other occupations. Younger health workers and people that spent longer periods of time ( $\geq 3$  h/day) had a higher prevalence of anxiety symptoms than those that spent less time ( $< 1$  h/day and 1–2 h/day) in the outbreak.

Huang and Zhao (2020a, 2020b) observed that medical support workers were more prone to poor quality of sleep compared with other occupational groups. The multivariate logistic regression showed that age ( $< 35$  years) and time spent focused on COVID-19 ( $\geq 3$  h per day) were associated with GAD and with medical support to workers that had a higher risk of poor sleep quality. Dai et al. (2020) pointed out that 4600 questionnaires were distributed. The main worries of health professionals are infection of coworkers (72.5%), infection of family (63.9%), protection measures (52.3%), and medical violence (48.5%). 39.1% of the health professionals had psychological suffering.

There is a correlation between COVID-19 and the development of mental disorders in health professionals. The linear relation was 0.72 (95% CI [0.66–0.78]) with a  $p$ -value  $< 0.01$ . In a logarithmic scale, there was a proportion higher than 70% for the selected cases (Figs. 2 and 3).

## 4. Discussion

Health professionals that work to fight COVID-19 are being more severely affected by psychiatric disorders (Lai et al. 2020; Zhang et al. 2020; Dai et al. 2020), sleep disorders (Huang and Zhao 2020a, 2020b; Qi et al. 2020), stress (Mo et al. 2020), and indirect traumatization (Li et al. 2020) than other occupational groups. After studying physiological and molecular reasons of psychiatric disorders more profoundly, we observed that somatic symptomatology culminates in psychoneuroimmunology bias analysis (PNI) of COVID-19 (Wang et al. 2020). The release of proinflammatory cytokines, including interleukin (IL) -1 $\beta$  and IL-6 of the respiratory tract, may be stimulated by the Severe Acute Respiratory Syndrome (SARS) caused by COVID-19 (Conti et al. 2020). In parallel, the increase of cytokines was also seen in major depression disorders and in functional somatic syndromes (Wang et al. 2020). Thus, COVID-19 and such psychiatric disorders have a similar psychoneuroimmunology (PNI) structure.

In this clinical scenario, the studies carried out by Lai et al. (2020) and Zhang et al. (2020) present higher statistically significant risks of a psychiatric symptomatology associated with depression, anxiety, distress, and insomnia in health professionals working in patients affected by COVID-19 in Wuhan, China. The results were obtained, respectively, through scales regarding the Patient Health Questionnaire (PHQ), the Generalized Anxiety Disorder (GAD), the Insomnia Severity Index (ISI), and the Impact of Events Scale-Revised (IES-R) (Lai et al. 2020).

The studies conducted by Zhang et al. (2020) and Lai et al. (2020) observed a higher statistically relevant prevalence in health professionals who are not doctors of symptoms of depression, anxiety, and insomnia; however, a new symptomatology associated with obsessive-compulsive traces and somatization was also reported. The organic presence of disease was an independent factor for insomnia, anxiety, depression, somatization, and obsessive-compulsive symptoms in doctors, but it was a risk factor for non-doctors (Zhang et al. 2020).

Despite insomnia reports in the outcomes found by Lai et al. (2020) and Zhang et al. (2020), more specific observations regarding sleep disorders were reported by Qi et al. (2020). Cross-sectional analyses

**Table 1**  
Summary of objectives, methodologies, results, and conclusions of the studies included for qualitative analysis in the systematic review based on the PRISMA method.

Author and year	Country	Objective	Method	Results	Conclusion
Zhang et al. (2020)	China	To explore if doctors had more psychosocial problems than other health workers during the COVID-19 outbreak	An online research was carried out with a total of 2182 Chinese participants. Mental health variables were assessed using the Insomnia Severity Index (ISI), the Symptom Checklist 90 Revised (SCL-90-R), and Health Questionnaire-4 (PHQ-4)	In comparison with health workers ( $n = 1255$ ), doctors ( $n = 927$ ) presented higher prevalence of insomnia (38.4 vs. 30.5%, $p < 0.01$ ), anxiety (13.0 vs. 8.5%, $p < 0.01$ ), depression (12.2 vs. 9.5%; $p < 0.04$ ), somatization (1.6 vs. 0.4%; $p < 0.01$ ) and obsessive-compulsive symptoms (5.3 vs. 2.2%; $p < 0.01$ )	During the COVID-19 outbreak, doctors presented psychosocial problems and risk factors for their development. They need mental health attention and recovery programs
Lai et al. (2020)	China	To assess the magnitude of results in mental health and associated factors among health professionals that treat patients exposed to COVID-19 in China	This cross-sectional paper was based on research and divided by region and collected demographic data and mental health measures of 1257 health professionals in 34 hospitals. Health professionals in hospitals equipped with clinics or nurseries for COVID-19 patients that were eligible	A considerable proportion of the participants reported depression symptoms (634 [50.4%]), anxiety (560 [44.6%]), insomnia (427 [34.0%]), and distress (899 [71.5%])	Participants reported having a psychological burden, especially female nurses and front-line health professionals involved directly in the diagnosis, treatment, and service to COVID-19 patients
Li et al. (2020)	China	To study the psychological stress, indirect traumatization caused by the COVID-19 pandemic in medical teams	The study used a total of 214 general audience and 526 nurses (i.e. 234 front-line nurses and 292 front-line nurses) to assess the indirect traumatization scores through a mobile app of questionnaire	The indirect traumatization scores for front-line nurses, including the scores and psychological responses, were significantly lower ( $p < 0.001$ )	Early strategies that aim to prevent and treat traumatization in the medical team are extremely necessary
Mo et al. (2020)	China	To investigate stress at work in Chinese female nurses during the fight against the 2019 Coronavirus disease (COVID-19) and to explore the relevant influence factors	Cross-sectional survey. An online questionnaire was filled out by 180 female nurses. Data collection tools, including the Chinese version of the Stress Overload Scale (SOS) and Self-Assessment Anxiety Scale (SAS)	The multiple regression analysis showed that children, work hours per week and anxiety were the main factors affecting nurses' stress ( $p = 0.000$ , 0.048, 0.000, respectively)	Nurses that fight against COVID-19 were, in general, under pressure
Qi et al. (2020)	China	To study the high mental stress in health professionals during the COVID-19 outbreak	An online questionnaire, including the Pittsburgh Sleep Quality Index (PSQI), Athens Insomnia Scale (AIS) and Visual Analogue Scale (VAS), was used to assess sleep disorders	A total of 1306 subjects was enrolled. A group of participants presented significantly higher scores of PSQI ( $p < 0.0001$ ), AIS ( $p < 0.0001$ ), anxiety ( $p < 0.0001$ ) and depression ( $p = 0.0010$ ) and higher prevalence of sleep disorders with PSQI > 7 points ( $p < 0.0001$ ) and AIS > 6 points ( $p = 0.0001$ )	The study showed that more than half of the professionals presented sleep disorders during the COVID-19 outbreak
Huang and Zhao (2020a)	China	To identify high-risk groups whose mental health conditions were vulnerable to the COVID-19 outbreak	Data were collected from 7236 selected participants measured through anxiety, depression symptoms and sleep quality	Health professionals have the highest rate of sleep disorders compared with other occupations. Younger health workers and people that spend longer time ( $\geq 3$ h/day) had a higher prevalence of anxiety symptoms than those that spend less time ( $< 1$ h/day and 1–2 h/day) during the outbreak	Continuous monitoring of psychological consequences to the high-risk population should become a routine as part of directed interventions during crisis
Huang and Zhao (2020b)	China	To assess the mental health burden of the Chinese during the outbreak and to explore the potential influence of the factors	A cross-sectional research. We collected data from 7236 assessed volunteers with demographic information, knowledge related to the COVID-19, generalized anxiety disorder (GAD), depression symptoms and sleep quality	In comparison with the other occupational group, medical support workers were more prone to poor sleep quality. The multivariate logistic regression showed that age ( $< 35$ years) and time spent focused on COVID-19 ( $\geq 3$ h per day) were associated with GAD and medical support. Workers were at high risk of poor sleep quality	Younger people, people that spent more time thinking about the outbreak, and health professionals had higher risk of mental disease
Dai et al. (2020)	China	This study aimed at investigating the risk perception and immediate psychological condition of health professionals in the initial stage of the COVID-19 epidemic	The General Questionnaire of Health was used to identify the immediate psychological status of participants. Risk perception and psychological status were compared by demographic characteristics and experiences of exposure to COVID-19	4600 questionnaires were distributed. The main worries of health professionals are infection of colleagues (72.5%), infection of relatives (63.9%), protection measures (52.3%), and medical violence (48.5%). 39.1% of health professionals had psychological suffering	In the fight against the COVID-19 epidemic, it was found that health professionals were worried with the infection risks and protection measures, which resulted in psychic suffering so that other actions were taken

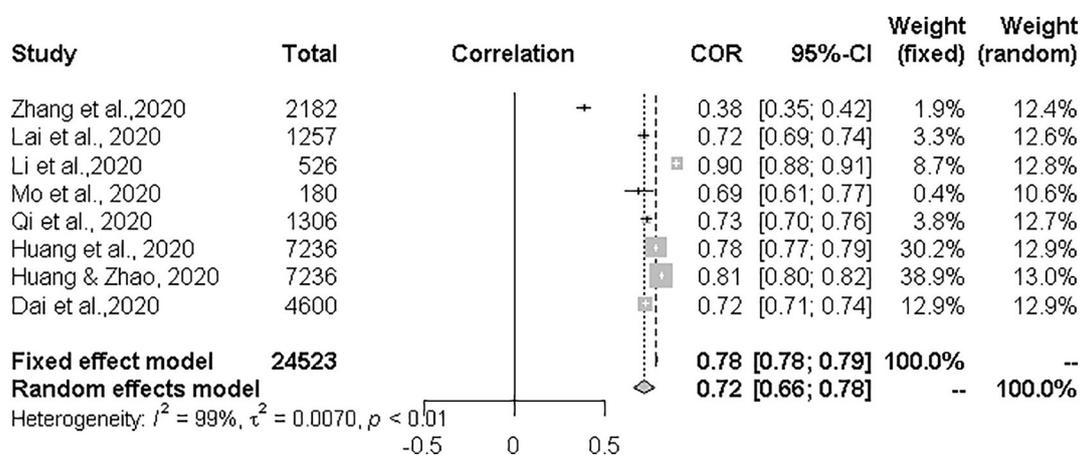


Fig. 2. Forest plot of meta-correlation between COVID-19 and psychiatric disorders in professionals.

pointed significantly higher indices for front-line medical workers regarding anxiety, depression, and sleep disorders, all with values of  $p < 0.0001$ . The indices were calculated through the Pittsburgh Sleep Quality Index (PSQI), Athens Insomnia Scale (AIS), and Visual Analog Scale (VAS) (Qi et al. 2020). By observing such disorders, health professionals in comparison with other occupational groups were pointed as more prone to poor quality of sleep. Multivariate logistic regression showed that health professionals had a high risk of poor quality of sleep (Huang and Zhao 2020a). Hence, a higher level of improper sleep was found among these health professionals compared with other occupations in a cross-sectional research (Huang and Zhao 2020b).

Dai et al. (2020) observations point a psychiatric symptomatology that was not previously discussed in Lai et al. (2020), Zhang et al. (2020), which is psychic suffering. This mental disorder was reported in 1704 (39.1%) of 4357 health professionals, mainly those working in Wuhan, taking part in first-line treatments, being isolated and having infected family members or coworkers. On the other hand, results show that indirect traumatization scores for front-line nurses, including scores for physiologic and psychologic responses were significantly lower than for nurses that do not belong to the front line. The indirect traumatization phenomenon was reported in cruel and destructive disasters, in which the level of damage exceeds the psychological and emotional tolerance and indirectly results in psychological

abnormalities. The main symptoms of indirect traumatization include loss of appetite, fatigue, physical decline, sleep disorders, irritability, inattention, numbness, fear, and despair (Li et al. 2020).

Regarding a higher predisposition or vulnerability to disorders among health professionals, the profiles of female nurses were significantly reported with more severe levels of all the measures of mental disorders (Lai et al. 2020). Being at risk of contact with patients, being a woman and living in rural areas were the most common risk factors for insomnia, anxiety, obsessive-compulsive symptoms, and depression (Zhang et al. 2020). In the analysis of subgroups of front-line medical workers, compared to the male gender, women also had a significantly higher prevalence of sleep disorders ( $p < 0.0001$ ) (Qi et al. 2020). A multiple regression analysis also showed that anxiety was significantly associated with stress developed by nurses whose fight against the COVID-19 pandemic makes them constantly under pressure.

Factors that stimulate the psychic conditions mentioned include work conditions to which health professionals are subjected to, such as performing tasks under great pressure, irregular work schedule, and long shifts, contributing to the development of psychological and sleep disorders (Sveinsdottir 2006). Besides the general stressors to which these professionals are exposed to, the COVID-19 pandemic context brings specific stressors, such as the risk of infecting yourself and others, the care of relatives socially isolated at home and worries about

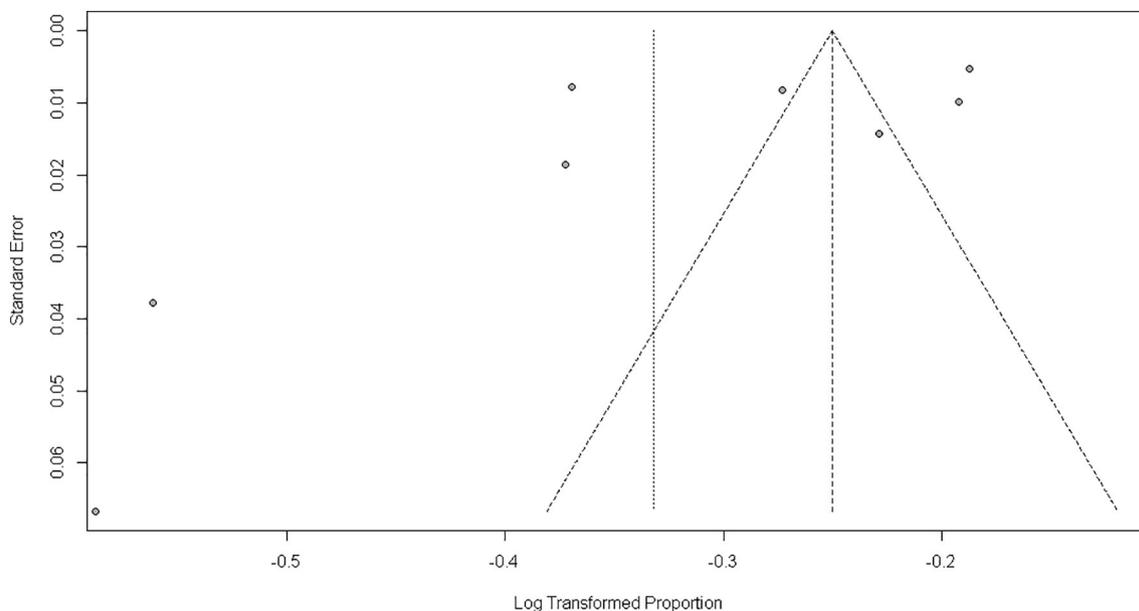


Fig. 3. Proportion of professionals with mental alterations.

mental and physical health conditions among coworkers (IASC, 2020). This prolonged exposure to stressors may exceed the mechanisms individuals have to fight back and this results in psychological repercussions for these subjects (Fava et al. 2019).

One of the causes of psychological stress among health professionals working in the pandemic may be associated with the difficulties found to ensure personal safety related to the high risk of being exposed to infected patients and the scarcity of protection equipment (Zhang et al. 2020). In addition, these professionals are seeing significant changes in their work environment, such as the increase of occupational responsibilities, strict measures of safety and reduced self-care due to lack of time and energy (IASC, 2020; WHO, 2020). In a cross-sectional study including 1306 health professionals in the province of Hubei, China, frequent work hours and occupational stress, besides COVID-19 severity, were mentioned by subjects as the main factors influencing sleep quality (Qi et al. 2020).

In turn, reduced social support received by these subjects due to long work hours and stigmatization of workers in contact with COVID-19 patients may also contribute to the professional stress of workers directly involved with the pandemic (IASC, 2020; WHO, 2020). This evidence is corroborated in the analysis of 4357 health professionals in China, which found that “being isolated” among many other factors was a factor associated with poor prognosis of psychological disorders (Dai et al. 2020). Similarly, working in rural areas was also associated with a higher risk of insomnia, anxiety, depression, and obsessive-compulsive disorder (OCD) among health professionals. This fact may also be associated with higher concerns about the risk of infection due to the need of working at a service that often has poorer work conditions in comparison with those from the urban area (Zhang et al. 2020).

Besides the psychiatric symptomatology analyses, some interventionist measures may contribute to reduce the stress suffered by health professionals and promote mental health improvement, even during the pandemic. At first, it is important to acknowledge violent emotions, under these circumstances, including anger, irritability or mood alterations. They should be seen as regular and comprehensible stress reactions and, therefore, should not be processed as guilty. Ensuring basic needs are duly satisfied is also especially important, besides having sufficient breaks, keeping a healthy diet and remaining physically active. The use of substances, like alcohol and tobacco, as a coping strategy may bring psychological and physical damage in the long term and should be avoided. Sharing experiences and feelings with colleagues experiencing similar problems may help reduce psychological stress. Telephone calls and message services can be used to keep social contacts in the private sphere, which is a great contributor to maintaining good mental health (WHO, 2020; IASC, 2020; Petzold et al., 2020).

The studies analyzed have limitations due to the limited scope, because most of the subjects belong to Wuhan, China, and due to the short period of the analysis. In addition, another limitation was the psychological assessments in online research and self-report tools. Therefore, large-sized longitudinal studies that include other health professionals, in addition to doctors and nurses, are necessary to further explore the pathogenesis, therapeutic strategies and use of clinical interviews to elaborate a wider assessment of the problem.

## 5. Conclusion

There is a strong association between health professionals and COVID-19 in terms of psychiatric repercussions. Our meta-analysis showed that health professionals have a higher level of indirect traumatization, in which the level of damage exceeds psychological and emotional tolerance, and indirectly results in psychological abnormalities. The incidence of obsessive-compulsive traces and somatizations was higher in situations involving front-line professionals. Hence, there are statistically significant risks for anxiety, depression, and sleep disorders in the fight against COVID-19, in which the causality still needs

to be elucidated. Cohort studies that are better designed or randomized clinical trials are, therefore, necessary to explore their most profound connections.

## Authors' contributions

MLRN and FCTS designed the review, developed the inclusion criteria, screened titles and abstracts, appraised the quality of included papers, and drafted the manuscript.

MLRN and FCTS reviewed the study protocol and inclusion criteria and provided substantial input to the manuscript.

MLRN and FCTS reviewed the study protocol. MLRN read and screened articles for inclusion. All authors critically reviewed drafts and approved the final manuscript.

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## Declaration of Competing Interest

The authors declare that they have no competing interests.

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