Suicidal Ideation of Healthcare Workers During COVID-19: An Ecological Momentary Assessment

Idéations suicidaires du personnel de la santé pendant la pandémie de COVID-19 : une évaluation écologique momentanée

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Résumé de l'article

Introduction : La pandémie de COVID-19 a eu un impact sur la santé psychologique des travailleurs de la santé (TS). Des études transversales rapportent la présence d'idées suicidaires chez cette population pendant cette période, mais aucune étude longitudinale n'a examiné l'évolution de ces idées dans le temps.

Objectifs : Évaluer l'évolution des idées suicidaires des TS au cours des deux premières vagues de la pandémie de COVID-19 au Québec (Canada) et identifier les facteurs de risque impliqués.

Méthodes : Une étude longitudinale, utilisant l'évaluation écologique momentanée, a été menée entre le 8 mai 2020 et le 31 mars 2021 (correspondant à la période entre la moitié de la 1re vague à la fin de la seconde) auprès des TS québécois. Les participants (n=865) ont répondu de façon hebdomadaire à des questions relatives à l'anxiété (GAD-7), à la dépression (PHQ-9), aux idées suicidaires (PHQ-9 Q.9), à l'exposition à la COVID-19, à l'exposition aux décès liés à la COVID-19, à leur statut infectieux et à celui de leurs collègues et de leurs proches, ainsi qu'au temps passé à consommer des nouvelles liées à la COVID-19.

Résultats : La proportion d'idées suicidaires a augmenté de mai à juin 2020 (deuxième moitié de la première vague) atteignant un pic à 18% avant de diminuer par la suite jusqu'en mars 2021. La gravité des symptômes d'anxiété et de dépression était corrélée positivement avec les idéations suicidaires, tout comme le fait d'avoir un collègue infecté à la COVID-19. Le soutien social ne semble pas être un facteur protecteur des idées suicidaires. Les idées suicidaires sont corrélées à la consommation de médias et un effet médiateur est observé par la présence d'une détresse clinique exprimée par des états dépressifs ou anxieux.

Discussion et conclusion : La consommation de médias dans un contexte de pandémie est associée à de l'anxiété et à de la dépression, dont les états les plus graves peuvent exprimer des idées suicidaires. Sans inférer un lien de causalité, il semble recommandé aux travailleurs de la santé de limiter leur exposition aux médias lors d'une catastrophe telle qu'une pandémie.
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Idéations suicidaires du personnel de la santé pendant la pandémie de COVID-19 : une évaluation écologique momentanée

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Introduction: The COVID-19 pandemic had an impact on the psychological health of healthcare workers (HCWs). Cross-sectional studies report suicidal ideation in this population during this period, but no longitudinal study has examined the evolution of these ideas over time.

Objectives: To assess the evolution of suicidal ideation of HCWs during the first two waves of the COVID-19 pandemic among Quebec (Canada) HCWs and to identify the risk factors involved.

Methods: A longitudinal study among Quebec (Canada) HCWs using ecological momentary assessment was conducted between May 8, 2020, and March 31, 2021 (corresponding to the second half of the first wave to the end of the second). Participants (n=865) answered weekly questions related to anxiety (GAD-7), depression (PHQ-9), suicidal ideation (PHQ-9 Q.9), exposure to COVID-19, exposure to COVID-19-related deaths, their infection status and that of their co-workers and loved ones, as well as the amount of time they spent consuming news related to COVID-19. Results: Proportion of suicidal ideation increased from May to June 2020 (second half of the first wave) peaking at 18% before declining up to March 2021. Anxiety and depression symptoms severity increased those ideations as well as having a colleague confirmed positive to COVID-19. Social support does not appear to be a protective factor for suicidal ideation. Suicidal thoughts are associated with media consumption and appear to be mediated by the presence of clinical distress expressed as depressive or anxiety states. Discussion and conclusion: Media consumption in a pandemic context is associated with anxiety and depression, the more severe states of which may express suicidal ideation. Without inferring causality relationship, it seems advisable for HCWs to limit their media exposure during a disaster such as a pandemic.
INTRODUCTION

Since the beginning of 2020, the COVID-19 pandemic has been disturbing the world, especially healthcare workers (HCWs), such as nurses who must learn to deal with this new virus and its consequences. This respiratory pandemic, like the previous ones linked to the severe acute respiratory syndrome known as SARS, is characterized by feelings of fear for one's health and that of others, higher stress at work, combined with isolation from one's social support system (Buselli et al., 2022; Chong et al., 2004). These factors contribute to increased stress in HCWs and can impact psychosocial functioning. More specifically, studies related to the mental health of HCWs during the pandemic period reported that they experience more depression, anxiety symptoms, acute stress, burnout, and avoidance (Al-Humadi et al., 2021; Alonso et al., 2021; Bismark et al., 2022; Vizheh et al., 2020). Moreover, two Canadian studies related to the impacts of the COVID-19 pandemic on mental health of HCWs report that more than one-third exhibit symptoms of depression, anxiety, or post-traumatic stress (Cyr et al., 2021; Dufour et al., 2022; Dufour et al., 2021). In addition, 52% of HCWs show symptoms associated with burnout, including emotional exhaustion and depersonalization (Cyr et al.; Dufour et al., 2022; Dufour et al., 2021).

Along with those impacts on the mental health of HCWs, it appears that the COVID-19 pandemic may influence the presence of suicidal ideation in this population. Indeed, a systematic review conducted between March 2020 and March 2021 (Buselli et al., 2022) reported that the prevalence of suicidal ideation among HCWs varied between 4 and 8%. Other studies published after March 2021 report rates of 10% in a Canadian HCWs population (n=86) (Wilbiks et al., 2021), 11% in an Australian population (n=7,795) (Bismark et al., 2022), and 14% in a Mexican population (n=5,938) (Robles et al., 2020). The way in which the presence of suicidal ideation was measured varied across studies, but the question 9 of the PHQ-9, which is an assessment tool for depression, has been shown to be reliable (Bismark et al.; Buselli et al.; Wilbiks et al.). All these studies were cross-sectional, so that the presence of suicidal ideation or suicidal behavior was measured at only one point. Given that the presence of suicidal ideation is a phenomenon that evolves over time, and because there were multiple waves associated with the COVID-19 pandemic, strategies such as ecological momentary assessment could provide a more accurate picture of this phenomenon (Kivelä et al., 2022).

Various risk and protective factors have been identified as potentially influencing suicidal ideation among HCWs in the pandemic context. Some of these risk factors, such as depression, poor mental health history, alcohol use, and previous suicidal behavior, are not specific to the pandemic context (Al-Humadi et al., 2021; Alonso et al., 2021; Bismark et al., 2022; Buselli et al., 2022). However, some risk factors that are more specific to the pandemic context, and which can particularly affect nurses who are at the forefront, also emerge in the literature, such as being exposed to COVID-19 patients, interacting with people with COVID-19, having been infected yourself, and having to isolate to protect others (Alonso et al.; Amsalem et al., 2021; Bismark et al.; Buselli et al.; Cai et al., 2021; Smallwood et al., 2022). Uncertainty about the virus or the fear of becoming infected or infecting loved ones are also factors that appear to increase the risk of suicidal ideation in HCWs (Awan et al., 2021; Cai et al.; Salman et al., 2020; Smallwood et al.). At the organizational level, lack of communication and coordination, lack of staff associated with increased workload, offloading, lack of personal protective equipment, and new tasks without training are also risk factors for suicidal ideation (Mortier et al., 2021; Robles et al., 2020; Salman et al.; Smallwood et al.). On the other hand, living with others and having children can act as protective factors against suicidal ideation.

The influence of suicide reporting on suicidal thinking and acting out has been the subject of numerous studies, which suggest that the relationship between suicide rates and media reporting (suicide stories reported in newspapers or on television) is causal and real (Domaradzki, 2021). Yet very few studies have looked specifically at the influence of the media on suicidal ideation.
during a pandemic. We know that media consumption during a global pandemic such as COVID-19 influences the mental health of the general population (Su et al., 2021). Moreover, the German study by Bendau et al. (2021) in the general population found that the frequent viewing of media content was positively correlated with anxiety \((r=0.25, p<0.001)\) and depression \((r=0.21, p<0.001)\) during the COVID-19 pandemic. Knowing that depression and anxiety are risk factors for suicidal ideation, it seemed crucial to see if consuming media during the COVID-19 pandemic is associated with increased suicidal ideation in HCWs.

**OBJECTIVES**

The purpose of this study was therefore to assess the evolution of suicidal ideation among HCWs during the COVID-19 pandemic and to identify the risk factors involved. More specifically, the objectives of this study were to 1) describe changes in the proportion of suicidal ideation in HCWs among a Quebec (Canada) sample and 2) identify risk factors, such as media consumption, that influence the rates of suicidal ideation among participants.

**METHODS**

This research project is an 11-month longitudinal study among Quebec HCWs using ecological momentary assessment (Kivelä et al., 2022). Data were collected through a mobile application (Ethica) between May 8, 2020, and March 31, 2021; period that corresponds to the middle of the 1st wave to the end of the second wave of the pandemic (Québec, 2022). Participants were asked to complete several questionnaires included in the application on a weekly basis. All responses were anonymous, confidential, and voluntary.

**RECRUITMENT**

Eight healthcare centres in the province of Quebec, Canada, participated in the study, mainly from the Greater Montreal area (4) and from other Quebec health regions: *Capitale-Nationale* (1), *Estrie* (1), *Montérégie* (1) and *Gaspésie-Île-de-la-Madeleine* (1). These settings represent the diversity of healthcare centers in Quebec, in both urban and rural areas, with or without an academic mission. Recruitment was carried out by contacting research coordinators in every clinical setting so they could distribute promotional material to their employees through various web-based platforms. Recruitment was continuous during the 11 months of the study which means that not all participants started using the application at the same time. No power calculation was done to determine the desired sample size. The project aims to recruit all participants who were available and willing to participate during the study period. Once the participants agreed to participate in the study and signed the consent form, sociodemographic data were collected. Upon answering the initial invitation, participants received a link to install a mobile phone application compatible with iOS or Android. Although the research project was initially designed to collect data over a 12-week period, participants were free to continue using the application thereafter.

A total of 865 HCWs participated in the study. Eighty-four percent of the responses came from participants in the Greater Montreal area, 8% from *Estrie* 6% from *Capitale-Nationale* and 2% from *Gaspésie-Îles-de-la-Madeleine*. HCWs were invited to participate in the study regardless of their title. Weekly, the application sent a notification inviting the participant to complete an online questionnaire. If the participant did not answer or only partially answered, they received a notification every 12 hours until they completed it. The duration of participation in the study varied greatly among participants; some completed the questionnaires for only one week (11.4%), while others responded for more than 40 weeks (0.2%). However, 55.6% of participants responded for at least 12 weeks and among all participants 34.7% responded for exactly 12 weeks. Because recruitment was continuous throughout the study and participation completely voluntary each week, the number of participants varied from week to week. The highest average weekly participation was between October and December 2020 (period corresponding to the 1st half of the second wave of the pandemic). Only those on sick leave for reasons
unrelated to COVID-19 at the time of recruitment were excluded.

**DATA COLLECTION**

In addition to the initial sociodemographic questions (age and gender), the application assessed symptomatology related to anxiety (General Anxiety Disorder, GAD-7) (Spitzer et al., 2006), depression, and suicidal ideation (Patient Health Questionnaire, PHQ-9) (Kroenke et al., 2001). Suicidal ideation was measured via question 9 of the PHQ-9, which reads: “In the past week how often have you been bothered by the thought that you would be better off dead or of hurting yourself in some ways” (Kroenke et al.). Results were interpreted according to the following clinical cut-off scores: 10 for the GAD-7 and 11 for the PHQ-9. When participants reached those cut-offs on the anxiety or depression scales, an automated message with local contact information for a resource center and help hotlines was provided. If suicidal ideation was detected, a specific message redirecting the user to urgent and non-urgent suicide resources was displayed. In this case, the research coordinator automatically received an email notification from Ethica. In this project, it was determined that participants with suicidal ideation included all those who answered other than ‘Never’ to question 9 of the PHQ-9.

The risk factors that were measured in this study were time spent consuming news about COVID-19, exposure to COVID-19 infected individuals, exposure to COVID-19-related deaths, infectious status of self, colleagues and loved ones, and the perceived availability of social support. To measure those factors, the application used a 4-level scale (almost never, sometimes, often, almost all the time) to assess the amount of time spent in the past week consuming news about COVID-19 in the media. Exposure to COVID-19-infected individuals and COVID-19-related deaths were to be reported weekly as well as the infectious status of self, colleagues, and loved ones. Perceived availability of social support was measured by an ad hoc questionnaire, with a 4-level scale (almost never, sometimes, often, anytime) addressing three aspects of social support (relatives, colleagues, and the organization).

**DATA ANALYSIS**

Descriptive analyses were carried out to draw up a portrait of the participants and to determine the proportion of participants reporting suicidal thoughts. For the depression score measure, Q.9 was removed from the score composition given that it served as a measure for suicidal ideation. A systematic review showed that there is a very strong correlation between PHQ-9 and PHQ-8 (which omits question 9) so that the same cutpoints can be used in research and clinical settings (Kroenke et al., 2010).

Subsequently, to conduct the analysis on the factors influencing suicidal ideation, a logistic regression model with random effects on the intercept was proposed. All analyses were done in R version 4.1.2 (R Core Team, 2022). Suicidal ideation was modeled as a generalized linear mixed-effect model using the binomial family because of the dichotomous nature of the suicidal ideation variable. A random-effect on the intercept was included to account for the intra-subject correlation. We used a linear mixed-effect models to model the data across time using package lme4 (Bates et al., 2015, p. 4). First, the effect of time was measured to determine how suicidal ideation changed over the duration of the study. The following variables were then included in a linear mixed-effect model with binomial distribution by a group of variables: 1) sex and age, 2) being in contact with a person infected with COVID-19, 3) awaiting COVID-19 test result, or being confirmed positive on a COVID-19 test, 4) contact with a deceased person, 5) consuming news on COVID-19, 6) social support, and 7) distress (GAD-7 score, and PHQ-8 score). All models were adjusted for decreasing time effect. Statistically significant variables were then combined into a single multiple linear regression model.

Finally, due to the results from the multiple linear regression model, a mediation test was conducted to test the indirect effect, through anxiety and depression variables, of time spent consuming news on suicidal ideation that passed. Standard Error and testing of the mediation were made using 1000 bootstrap resampling. This approach (Preacher & Hayes, 2008) is preferred over the traditional methods because it gives more accurate results. The mixed model handled the
missing data by using the maximum likelihood estimation method.

**ETHICAL CONSIDERATIONS**

This study was given approval by the research ethics board of the Centre hospitalier de l'Université de Montréal Research Center (20.015).

**RESULTS**

Most participants were women (88%) with a mean (SD) age of 39.7 (10.0). The proportion of suicidal ideation, measured between May 2020 (middle of the 1st wave) and March 2021 (end of the 2nd wave), ranged from 6 to 18%, with higher proportions in June and July 2020 at 18% and 16%, respectively. Figure 1 shows the change in the proportion of suicidal ideation among participants throughout the study. The effect of the time variable is statistically significant ($\beta = -2.4935$, $p < 0.001$) and for each month that passes, the risk of presenting suicidal ideation is divided by 12.

As for the other variables studied, gender ($\beta = 0.16$, NS), age ($\beta = 0.05$, NS), contact with an infected person ($\beta = 0.25$, NS), contact with a deceased person, whether a patient ($\beta = 0.78$, NS), a colleague ($\beta = -0.97$, NS), a relative ($\beta = 1.57$, NS) or an acquaintance ($\beta = -0.10$, NS) and perceived social support from relatives ($\beta = -0.22$, NS), colleagues ($\beta = -0.11$, NS) and the organization ($\beta = -0.05$, NS), were not statistically significant. However, having a colleague infected with COVID-19 was positively and significantly associated with suicidal ideation ($\beta = 0.68$, $p < 0.05$). In addition, time spent consuming news related to COVID-19 was also positively associated with suicidal ideation ($\beta = 0.35$, $p < 0.01$) indicating that for every one unit increase on the 4-level scale of news consultation the risk of having suicidal ideation increases by 1.4. For anxiety ($\beta = 0.14$, $p < 0.001$) and depression ($\beta = 0.33$, $p < 0.001$); both were positively associated with suicidal ideation. The risk was multiplied by 1.2 for each one-unit increase on the anxiety scale and by 1.4 for each one-unit increase on the depression scale.

Once the significant variables were included in the final multivariate model, only the variables of time ($\beta = -1.27$, $p < 0.05$), anxiety ($\beta = 0.14$, $p < 0.001$) and depression ($\beta = 0.16$, NS) remained statistically significant. Thus, based on the multivariate model, the risk of reporting suicidal ideation decreases over time while anxiety and depression scores are positively associated with the risk of presenting suicidal ideation. All these results from the logistic regression models are presented in Table 1. As for the mediation test, it appears that the effect of media consumption was associated with an increase in anxiety ($\beta = 1.00$, $p < 0.001$) and depression ($\beta = 0.95$, $p < 0.001$). Thus, Figure 2 demonstrates a complete mediation indicating news consumption has an indirect effect on suicidal ideation.

**Figure 1**

*Proportion of suicidal ideation between May 2020 and March 2021*
Table 1

Results from generalized linear mixed-effect model with binomial distribution of factors related to suicidal ideation

<table>
<thead>
<tr>
<th>Group</th>
<th>Variable</th>
<th>Suicidal ideation by group of variables</th>
<th>Suicidal ideation final multivariate model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Estimate</td>
<td>Standard error</td>
</tr>
<tr>
<td>1</td>
<td>Sex (Men)</td>
<td>0.16</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>Age/10</td>
<td>0.05</td>
<td>0.21</td>
</tr>
<tr>
<td>2</td>
<td>Contact with a person infected from Covid-19</td>
<td>0.25</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>Waiting for a result</td>
<td>0.11</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>Confirmed positive</td>
<td>2.12</td>
<td>1.11</td>
</tr>
<tr>
<td>3</td>
<td>Colleague confirmed positive</td>
<td>0.68</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>Loved one confirmed positive</td>
<td>0.00</td>
<td>0.51</td>
</tr>
<tr>
<td>4</td>
<td>Deceased patient</td>
<td>0.78</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>Deceased colleague</td>
<td>-0.97</td>
<td>2.17</td>
</tr>
<tr>
<td></td>
<td>Deceased loved one</td>
<td>1.57</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>Deceased relative</td>
<td>-0.10</td>
<td>0.55</td>
</tr>
<tr>
<td>5</td>
<td>Consuming news about Covid-19</td>
<td>0.35</td>
<td>0.11</td>
</tr>
<tr>
<td>6</td>
<td>Support from loved ones</td>
<td>-0.22</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Support from relative</td>
<td>-0.11</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>Support from organisation</td>
<td>-0.05</td>
<td>0.13</td>
</tr>
<tr>
<td>7</td>
<td>GAD-7</td>
<td>0.14</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>PHQ-9 (without Q.9)</td>
<td>0.33</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Note. All models were adjusted for the decreasing time effect. The first series of analyses include models by a group of variables: 1) Sex and age, 2) Contact with a person infected from Covid-19, 3) Testing for Covid-19, 4) Contact with a deceased person, 5) Consuming news on Covid-19, 6) Social support, 7) Distress.
**DISCUSSION**

The results of this study revealed that the proportion of suicidal ideation among HCWs participants fluctuated from 6 to 18% from the second half of the first wave to the end of the second wave of COVID-19 in the province of Quebec (Canada). This finding is higher than those currently found during the COVID-19 pandemic context (Alonso et al., 2021; Bismark et al., 2022; Buselli et al., 2022; Vizheh et al., 2020), except for one American study where a 19% proportion of suicidal ideation was reported between September and December 2020 (Amsalem et al., 2021).

This study also identified that time is a factor inversely correlated with suicidal ideation in HCWs. The highest proportion coincides with the end of the first wave, then decreased over time. The early phases of the pandemic were obviously more stressful due to the high level of threat and uncertainty. The effect of the lockdown that ended in late May in Quebec may also explain a gradual decrease of suicidal thoughts even though the restrictive measures that were intensified again in October 2021 do not seem to have had an effect. As the pandemic continued to evolve with an increased pressure experienced in the work environment, the pandemic fatigue, and the exhaustion of the staff (Costa et al., 2022; Smallwood et al., 2022), it would have been interesting to observe if an upsurge in suicidal ideation happens. It is plausible to envisage such a hypothesis since the fatigue and exhaustion experienced by professionals, including nurses, could lead to a feeling of powerlessness. This feeling of powerlessness is also associated with suicidal ideation in the interpersonal theory of suicide (Hagan et al., 2015; Smallwood et al.). Unfortunately, data collection ended at the end of the second wave.
Concerning the factors associated with suicidal ideation in HCWs, it is not surprising to find symptoms of anxiety and depression here. Indeed, these two psychological outcomes are known risk factors for suicidal ideation (Bentley et al., 2016; Turecki & Brent, 2016). However, social support did not act as a protective factor for suicidal ideation among HCWs in this study even though it is recognized as a protective factor (Turecki & Brent). This difference could be explained by the fact that, in the context of the COVID-19 pandemic, some studies report that the fear of infecting others may cause some HCWs to avoid social contact and socially stigmatize themselves as potential sources of infection making social support unavailable (Cabarkapa et al., 2020; Robles et al., 2020; Salman et al., 2020). Finally, we found that exposure to news related to COVID-19 could have an indirect effect on suicidal ideation through its effect on anxiety and depression. Indeed, exposure to bad news during the COVID-19 pandemic and its effect on negative emotions has been discussed in several studies (Giri & Maurya, 2021; Su et al., 2021). However, the link with suicidal ideation had not been previously raised.

Research on the relationship between disaster media coverage and psychological health suggests that media coverage has a negative influence on psychological health with no clear clinical or long-term adverse effect (Pfefferbaum et al., 2014). Although graphic images of mass trauma have more deleterious effects (Holman et al., 2020), it is possibly the recurrence of images of death and uncertainty that may have played a role during the pandemic. In addition, continued exposure during off-duty hours may have influenced distress and ultimately suicidal ideation of healthcare workers, including nurses. Not to mention individuals who are already distressed but may consume more media to obtain information and to calm down or even maintain their heightened arousal. In such a context, it could be interesting for managers to encourage nurses and other health professionals to follow a media diet to avoid overexposure.

The results of this study also encourage healthcare settings to be on the lookout for professionals who show more distressing symptoms, such as isolation, irritability, behavioral changes during a pandemic because they are at greater risk for suicidal ideation. Work organizations can support distressing healthcare workers in several ways. First, healthcare workers should be encouraged to reconnect with themselves, which can be done through self-monitoring as was proposed in this study by a mobile application available on the worker’s cell phone. Second, the use of attentive and caring (even trained) peers/colleagues to accompany distressed workers is a strategy that should be organized and sustained by healthcare settings. Finally, a work environment that empowers workers and provides simple, concrete measures of well-being such as flexible schedules, safe physical spaces, rest areas (Chen et al., 2020) is another way to prevent and support psychological distress.

**Strengths and Limitations**

The use of the ecological momentary assessment to evaluate suicidal ideation in HCWs during the COVID-19 pandemic is a strength of this study. However, the type of recruitment did not allow us to determine the number of people to whom the invitation was sent, which prevents us from knowing the response rate. In addition, since it was a self-reported questionnaire, participants may have minimized or exaggerated their symptoms. Finally, it is important to remember that this is a provincial representation of the HCWs experience. It is not possible to generalize these data to all of Canada and other countries due to the provincial and international differences that exist such as the healthcare system organization and the magnitude of the pandemic crisis.

**Conclusion**

At the end of the first wave of COVID-19 in Quebec, up to 18% of HCWs reported suicidal ideation. Anxiety, depression and news consumption were factors that were positively associated with suicidal ideation. In order to prevent suicidal ideation, work organizations can play a role by being alert to workers presenting symptoms of distress and by providing a work environment that promotes worker empowerment.
Authors’ contribution: SGe, NB and SGu conceptualized, designed and contributed to data acquisition. CG, SGe and MMD contributed to data interpretation. EPT, CG and SGe first draft the manuscript. All authors significantly contributed to the revision of the manuscript and approved its final version.

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